# Kongeriget Danmark

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Patent- og Varemærkestyrelsen
Kongeriget Danmark

**Patent- og Varemærkestyrelsen**
Erhvervsministeriet

Taastrup, 10 July 2001

Karin Schlichting
Head Clerk

# Pharmac utical kit comprising mid drine as active ingredient

## Introduction

The present invention relates to a method for treating patients with a novel controlled release pharmaceutical compositions for oral use containing midodrine and/or its active metabolite desglymidodrine together with a fast onset composition of midodrine and/or its active metabolite desglymidodrine. The invention also relates to a kit comprising the controlled release composition for once or twice daily administration together with one or more fast onset composition for supplemental and individual administration.

The novel sustained release compositions are designed to release midodrine and/or desglymidodrine after oral intake in a manner which enables absorption to take place in the gastrointestinal tract so that a relatively fast peak plasma concentration of the active metabolite desglymidodrine is obtained followed by a prolonged and relatively constant plasma concentration of desglymidodrine. However, the patient may due to individual needs or because of activities during the day experience situations where an increase in the plasma concentrations is needed for an optimal treatment regimen. Therefore, the patient may on an individual basis supply the sustained release composition with one or more administrations of a quick release formulation or any other formulation providing a fast onset.

The indications of Midodrine includes orthostatic dysregulation, constitutional and symptomatic hypotension (e.g. hypotionsion associated with infections, the convalescent period, surgical operations, delivery, changes in the weather as well as what is called "difficulties in getting started in the mornings"), as well as in the control of hypotensive side effects of hypnotics and psychotropics. Futhermore, Midodrine is expected to be effective in the treatment of urinary incontinence. Many of these indications call for a very individual treatment regimen where a basic "all day" treatment supplied with one or more fast onset formulations is very beneficial.

In another aspect, the invention relates to a method for treating hypotension and/or urinary incontinence, the method comprising administration to a patient in need thereof of an effective amount of midodrine and/or desglymidodrine in a sustained composition

according to the invention together with one or more fast onset compositions comprising an effective amount of midodrine and/or desglymidodrine.

One of the advantages of the invention is therefore that the sustained release formulation provides a base line plasma concentration which during most of the day is therapeutically effective. When a higher concentration is needed, only a minor supply of active ingredient is necessary to obtain a very fast relief from symptoms. If the constant base line plasma concentration were absent, it would be necessary to use a relative higher fast onset dose to reach the high therapeutically effective level. The high therapeutically effective level may be due to individual circumstances in the patient or may be a consequence of physical routines and the nature of the underlying disease. The situations and symptoms is often well recognized and experienced by the patient himself. The kit according to the present invention is a superior tool for obtaining an optimal treatment with a minimum of active ingredient.

The novel sustained release compositions are designed for administration once or twice daily, preferably once daily, i.e. a therapeutically effective concentration of desglymidodrine is maintained for a period of at least 10-16 hours followed by a wash out period of about 8-12 hours in order to avoid the well-know midodrine related side effect with respect to supine hypertension.

Background of the invention

Controlled release midodrine compositions are known from the prior art, e.g. US-A-5,128,144 (Korsatko-Waabnegg et al.), EP-B-0 164 571 (CL Pharma Aktiengesellschaft) and AT-B-383 270 (Chemie Linz Aktiengesellschaft). However, in none of these documents are any compositions intended for administration once daily and furthermore, there is no indication of absorption of midodrine (or its active metabolite) from the colon.

Disclosure of the invention

Midodrine is a prodrug which is activated within the human body by a rapid enzymatic hydrolysis to release the therapeutically active metabolite desglymidodrine. Desglymidodrine acts by a stimulation of $\alpha_1$ receptors. Midodrine is used in the treatment of conditions such as,e.g.,

Orthostatic regulatory disorders and dysfunctions; constitutional hypotension; symptomatic hypotension during convalescence, after surgical interventions and following child birth; hypotensive lability due to weather sensitivity and foehn complaints; difficulties in getting started in the morning; adjuvant in urinary stress incontinence (mainly 1st and 2nd degree, subdivision according to Ingelman-Sundberg); retrograde ejaculation; disorder of semen ejaculation; severe orthostatic hypotension in connection with degenerative neurological diseases; hypotension due to therapy with psychotropic drugs; reduction of blood pressure due to treatment with neuroleptics and antidepressives; intrinsic hypotension; idiopathic orthostatic hypotension; and severe orthostatic hypotension.

Furthermore, midodrine may be used to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Egglesten, Shy-Drager syndromes, diabetes mellitus disease and Parkinson's disease.

Midodrine is approved in a variety of European and overseas countries including the U.S.A. mainly for the treatment of orthostatic hypotension.

FDA has recommended a dosing of midodrine of up to 10 mg 3 times daily for the treatment of hypotension. According to FDA , the latest dose must not be given later than 6 pm for safety reasons in order to avoid or reduce the risk of supine hypertension. Other countries recommend that the latest dose must not be given later than 4 hours before bedtime.

Midodrine for use in stress urinary incontinence is a very promising use with a tremendous market potential also due to the ageing population. Current conservative therapeutic approaches are either $\alpha$-sympathomimetics, pelvic floor exercises and estrogens and surgery which are rather complementary than competitive.

With respect to mild to moderate form of orthostatic hypotension, midodrine has a considerably larger market potential than the severe form only.

Due to the rather short half-life of the active metabolite of approximately 3 hours midodrine normally must be administered 2-4 times daily. Considering the chronic nature of the diseases in question which requires a long term treatment as well as the correlation between plasma levels and the incidence and severity of adverse events, the development of a controlled release form is highly desired.

It has now been found that absorption takes place through the whole gastrointestinal tract. Thus, it has been found that when midodrine is applied to colon (about 8 hours after intake of a single unit capsule containing midodrine) the prodrug midodrine is not measured in plasma at least not at a therapeutic level while the extent of absorption of the active metabolite identical to that of a solution. In other words, with respect to absorption from the colon it has been found that it is not midodrine which is measured after oral intake of midodrine but instead it is the active metabolite desglymidodrine itself.

After colon application a maximum plasma concentration of desglymidodrine is found to take place at approximately 3 hours after application, i.e. $t_{max}$ corresponds to approx. 3 hours. In contrast thereto, a $t_{max}$ of about 1 hour for desglymidodrine is observed after oral intake of midodrine and the corresponding value for midodrine itself is a $t_{max}$ of about 30 min.

The finding that midodrine is converted to the active metabolite before or during absorption from the colon is of importance with respect to the present invention. A further important issue is the fact that FDA has recommended that the latest dose of midodrine is taken not later than 6 pm for safety reasons, thus a wash out period through the night is desirable.

The invention is based on the above findings. Thus, the present inventors have developed a pharmaceutical kit comprising as one part a controlled release composition for oral use containing midrodrine and/or desglymidodrine and the composition is designed to the release of midodrine and/or desglymidodrine it at least the following consecutive steps:

1. an initial relatively fast release of midodrine and/or desglymidodrine (in order to obtain a relatively fast onset of action),
2. an steady release of midodrine and/or desglymidodrine (in order to maintain a plasma concentration of desglymidodrine which is prolonged and relatively constant),
3. a second rise in release rate of midodrine and/or desglymidodrine (in order to take advantage of absorption from the colon, i.e. such a second release is designed to take place when the composition (or the disintegrated parts of the composition) reaches the colon; normally this takes about 8 hours after oral intake, and
4. a decline in release rate corresponding to that essentially all midodrine and/or desglymidodrine have been released from the composition.

The above release pattern is contemplated in order to obtain a desired plasma concentration of desglymidodrine during day and night after administration orally once daily. Thus, the release pattern above is based on the following requirements with respect to the plasma concentration of desglymidodrine:

1. an initial rise in plasma concentration until a peak concentration is reached,
2. a relatively constant plasma concentration of desglymidodrine for approximately about 6-14 hours such as, e.g. for at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours or at least about 12 hours.
3. a decline in plasma concentration with a half-life of about 3-4 hours to avoid supine hypertension.

Compositions according to the invention are therefore designed based on the following principle; the term part is intended to include a separate part within the composition (the composition may contain pellets of e.g. two different types, or an integrated element of the composition, e.g. a multilayer tablet):

1. The composition contains a part intended for relatively fast release of midodrine and/or desglymidodrine

2. The composition contains a part intended for prolonged release of midodrine and/or desglymidodrine and the prolonged release is intended to last for at least about 7-8 hours.
3. The composition contains a part intended to release midodrine and/or desglymidodrine relatively fast when the composition (or the disintegrated parts of the composition) reaches the colon, i.e. about 6-10 hours such as, e.g., about 8 hours after oral administration.

4. The release of midodrine and/or desglymidodrine from a composition according to the invention is terminated at the most about 12-16 hours after administration in order to obtain a wash out period during night.

In one aspect the kit according to the invention relates to a controlled release pharmaceutical composition for oral use comprising midodrine or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof,

the composition being adapted to release midodrine and, when present, desglymidodrine in such a manner that a relatively fast peak plasma concentration of desglymidodrine is obtained and that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 9 hours such as, e.g. at least about 10 hours, at least about 11 hours., at least about 12 hours, at least about 13 hours, at least about 14 hours or about 14 hours.

More specifically, a relatively fast peak plasma in the concentration of desglymidodrine is obtained about 15 min - 3 hours such as, e.g. about 0.5-1.5 hours or about 1 hour after oral administration of a composition according to the invention.

As mentioned above, it is important to keep the plasma concentration at a relatively constant level and, therefore, the plasma concentration of desglymidodrine after administration of midodrine and/or desglymidodrine is preferably maintained at a therapeutically active level for about 6-16 hours such as, e.g. about 7-16, about 8-15, about 9-15, about 10-15, about 11-14, about 12-14 or about 13, or for at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about

10 hours, at least about 11 hours, at least about 12 hours, at least about 12 hours, at least about 13 hours or at least about 14 hours.

Furthermore, the plasma concentration of desglymidodrine is preferably maintained at a relatively constant level for about 6-14 hours such as, e.g. for at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours or at least about 12 hours.

In the present context, the term "relatively constant level" means that n is n ± 30% and wherein n is the plasma concentration in ng/ml and monitored in a healthy person.

It should be noted that the initial fast release from the controlled release composition may be replaced by a separate fast onset formulation resulting in a peak plasma concentration within the period stated above for the initial rise in plasma concentration.

In principle, relevant active drug substances for use in kit according to the invention are any drug substance which is subject to colon absorption. The most interesting drug substances in this respect and with respect to treatment of orthostatic hypotension and urinary incontinence are the prodrug midodrine and its active metabolite desglymidodrine. In a preferred aspect, a composition according to the invention includes midodrine alone, desglymidodrine alone, or a combination of midodrine and desglymidodrine. Of course such compositions may also contain other active drug substances, if relevant.

Generally, after oral administration of a controlled release composition according to the invention containing midodrine, a peak plasma concentration of midodrine is obtained 15-90 min after oral administration. Moreover, the plasma concentration of midodrine after oral administration is maintained at a relatively constant level for about 6-11 hours such as, e.g. at least about 6 hours, at least about 7 hours or at least about 8 hours. To this end, the term "relatively constant" is intended to mean m ± 30% and wherein m is the plasma concentration in ng/ml and monitored in a healthy person.

The fast onset formulations may be in the form of conventional tablets, solutions, suspensions, gels, nasal formulations, formulations for pulmonary administration, chewing formulations such as chewing gum, wafers etc. Preferred formulations for a fast onset is nasal formulations as well as quick release formulations.

In a further aspect of the invention, a transdermal patch may replase the fast onset formulation in that transdermal patches may provide the necessary supply of active drug in a very convenient manner for the patient.

In the following further details on a controlled release composition according to the kit of the invention are given.

Details of the fast onset formulation is given in Examples 11 -17

Dissolution requirements

As described in the following, a target plasma profile and release profile can be designed for midodrine and the active metabolite desglymidodrine.

Based on our knowledge of the plasma profile of a midodrine solution and obtained $C_{max}$ values for inactive midodrine and active metabolite desglymidodrine after tablet administration a target *in vivo* profile has been estimated (Figs. 1 and 2).

The target profile is based on the findings discussed above and the assumption that it would be preferable to have a fast onset of action and a stable plasma level for 8-11 hours and thereafter to eliminate the drug during the night phase to avoid supine hypertension.

The presumptions made in estimating this target profile were:

i) a fast peak and an effective concentration of the active metabolite for approximately 14 hours are desired from a therapeutic point of view (FDA recommendation: lastest dose at 6 pm)

ii) that the first fraction of the composition should have an absorption rate similar to that of plain tablets

iii) that the peak concentration should not be higher than the peak concentration observed after administration of 33% of the total dose in the form of a plain tablet, and

iv) that the plateau level for midodrine should last for approximately 8 hours and for desglymidodrine for approximately 11 hours

v) that the drug reaches colon after approximately 8 hours

vi) that midodrine is absorbed in the colon with a $t_{max}$ of 3 hours (desglymidodrine) compared to a $t_{max}$ of ½ hour (midodrine) when absorbed in the small intestine

vii) that midodrine will not be measured after the colon absorption as midodrine but only as desglymidodrine

viii) that $t_{max}$ of desglymidodrine will appear 1 hour after oral administration of midodrine

ix) that $t_{½}$ for midodrine is ½-1 hour and for desglymidodrine 3-4 hours

x) that $C_{max}$ after 7.5 mg midodrine is approximately 11 ng/ml (midodrine) and approximately 3.75 ng/ml (desglymidodrine)

A person skilled in the art is capable of determining the actual values with respect to the above-mentioned provisions and based on such values perform any necessary correction to the estimated profile (target profile).

Based on the fact that midodrine plain tablets are dosed from 2.5 mg - 10 mg up to 4 times daily and that an individual variation in need for midodrine is known, the level of the target plasma profile may vary a factor 0.1-5. The shape of the profile is more important than the exact level of plasma concentrations.

The estimated target plasma profile has been deconvoluted with plasma concentrations from an oral solution for both midodrine and desglymidodrine to give an estimated *in vivo* dissolution profile (Figs. 3 and 4). All data were normalised to a dose of 7.5 mg before deconvolution. In the deconvolution a time interval of 0.5 hours was employed (cf: Langenbucher F, Möller H. Correlation of *in vitro* drug release with *in vivo* response kinetics. Part I: mathematical treatment of time functions. Pharm Ind 1983;45:623-8 and

Langenbucher F, Möller H. Correlation of *in vitro* drug release with *in vivo* response kinetics. Part II: Use of function parameters. Pharm Ind 1983;45:629-33).

The presumption in making this deconvolution was that the daily dose of midodrine is the same irrespective of whether the new CR composition or a plain tablet or a solution were administered.

Using this deconvolution, the *in vitro* dissolution profile for a composition according to the invention is estimated.

Presumptions for this estimation are:

i) that the *in vitro – in vivo* correlation will be 1:1

ii) that it is possible with the new invention to make a product with essential 100% release after 10-14 hours

iii) that midodrine is absorbed as such or as the active metabolit through the whole gastrointestinal tract (including colon) in order not to loose any amount of active drug substance ready for absorption into the circulatory system.

Target release *in vitro* profile estimated as described above:

| Time (hours) | % w/w released midodrine |
|---|---|
| 0.5 | 25 |
| 1 | 35 |
| 2 | 39 |
| 3 | 47 |
| 4 | 53 |
| 5 | 60 |
| 6 | 66 |
| 7 | 73 |
| 8 | 80 |
| 9 | 87 |
| 10 | 93 |
| 12 | 100 |

In order to reflect the second release of midodrine corresponding to the time when the composition reaches the colon, the following target profile is also relevant:

| Time (hours) | % w/w released midodrine |
|---|---|
| 0.5 | 25 |
| 1 | 35 |
| 2 | 39 |
| 3 | 47 |
| 4 | 53 |
| 5 | 60 |
| 6 | 66 |
| 7 | 75 |
| 8 | 90 |
| 9 | 95 |
| 10 | 97 |
| 11 | 99 |
| 12 | 100 |

As apparent from the above, a relatively fast release of midodrine is suitable and after about 6-8 hours a second rise in release should be observed. Accordingly, a target release rate profile is as follow (the release rate is given in % dissolved/hour):

about 35 %/hour about 30 min after start of the dissolution test,
about 12 %/hour about 1 hour after start of the dissolution test,
about 6 %/hour about 2 hours after start of the dissolution test,
about 7 %/hour about 3 hours after start of the dissolution test,
about 6.5 %/hour about 4 hours after start of the dissolution test,
about 6.5 %/hour about 5 hours after start of the dissolution test,
about 7.5 %/hour about 6 hours after start of the dissolution test,
about 12 %/hour about 7 hours after start of the dissolution test,
about 10 %/hour about 8 hours after start of the dissolution test,
about 3.5 %/hour about 9 hours after start of the dissolution test

about 2 %/hour about 10 hours after start of the dissolution test,
about 1 %/hour about 12 hours after start of the dissolution test.

In Fig. 5 is given a target dissolution profile and a target release rate curve.

As dissolution test any acceptable method may be applied, preferably a method according to USP or Ph.Eur. Throughout the examples, the following method has been employed: the *in vitro* dissolution method according to USP and Ph.Eur. employing dissolution apparatus 2 (paddle), 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C. It is contemplated that other dissolution media may be suitable as well as another rotation speed.

Reference is given to the claims herein where further details concerning the dissolution patterns and the release rates of a composition according to the invention are given.

Active drug substances

As mentioned above, a kit according to the invention is suitable for use for any active drug sustance which is subject to colon absorption and which beneficially can be administered only once or twice daily.

With respect to treatment of orthostatic hypotension and the other conditions mentioned above, midodrine and its active metabolite desglymidodrine are drugs of choice.

Midodrine as well as desglymidodrine exist in racemic form and in the form of the two enantiomeric species.

A kit according to the invention may therefore include midodrine in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

In an embodiment according to the invention a controlled release composition and/or fast onset formulaion includes at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of midodrine in the therapeutically active enantiomeric form; and the therapeutically active enantiomeric form of midodrine is (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide or the (R) form of midodrine.

In another embodiment according to the invention, a controlled release composition and/or a fast onset formulation contains the active metabolite desglymidodrine (ST 1059), and desglymidodrine is present in the form of (±)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (± ST 1059), (+)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (+ ST 1059), (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or mixtures thereof.

In a still further embodiment a controlled relase composition and or the fast onset formulaton according to the kit of the invention contains desglymidodrine in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof, or it contains at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of desglymidodrine is present in the therapeutically active enantiomeric form. The therapeutically active enantiomeric form of desglymidodrine

is cont mplated to be (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or the (R) form of desglymidodrine ((R) ST 1059).

In a controlled relase composition of the kit according to the invention midodrine and/or desglymidodrine are present in the form of a pharmaceutically acceptable salt such as a salt formed between midodrine and/or desglymidodrine and an inorganic acid such as e.g., a hydrochoride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a $H_3PO_3$ salt, a $H_3PO_4$ salt, a $H_2SO_3$ salt, a sulfate, a $H_2SO_5$ salt, or a salt formed between midodrine and/or desglymidodrine and an organic acid such as organic acids like e.g. $H_2CO_3$, acetic acid, $C_2H_5COOH$, $C_3H_7COOH$, $C_4H_9COOH$, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid

Dosage

In general, the dosage of the active drug substance present in a controlled composition according to the kit of the present invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

A controlled composition according to the kit of the present inventions aims at a dosage once or twice daily, preferably once daily. In the present context the term "once daily"/"once-a-day" is intended to mean that it is only necessary to administer the pharmaceutical composition once a day in order to obtain a suitable therapeutic and/or prophylactic response; however, any administration may comprise co-administration of more than one dosage unit, such as, e.g. 2-4 dosage units.

In agreement with the above-mentioned definition of "once daily"/"once-a-day", "twice daily"/"twice-a-day" is supposed to mean that it only necessary to administer the controlled pharmaceutical composition of the kit at the most twice a day in order to obtain a suitable therapeutic and/or prophylactic response in the patient which can form a basis for the individua supply with the fast onset formulation.

Irrespective of the above-mentioned definitiones of "once" and "twice" daily, a dosage unit constructed to deliver the active ingredient after only one daily administration is preferred. However, due to individual circumstances some patients may ne d a new dosage after

.g. 12 or 18 hours if the patient e.g. has abnormal absorption or bowel transit time. If the individual has a relatively fast bowel transit time, some of the active drug substance may be excreted before the full dosage is released.

With respect to midodrine, the normal daily dose is from 2.5 to 10 mg three or up to four times daily (calculated as midodrine hydrochloride), i.e. a daily dose of from about 7.5 mg to about 30 mg in the treatment of orthostatic hypertension. However, the daily dose in the treatment of urinary incontinence may be different and, accordingly, a controlled release composition according to the present invention typically contains from about 2.5mg to about 50 mg midodrine such as, e.g. 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg. In the cases, where midodrine is employed in another form, e.g. in another salt form than midodrine hydrochloride, the above-mentioned dosage ranges are of course to be recalculated so that the same dosage is employed on a molar basis.

The total daily doses of midodrine will depend on the indication for the treatment and the individually tolerated doses. The kit of the present invention provides a possibility of a treatment regimen adapted for the specific patient.

The individual fast onset doses of the kit of the invention may be from 0.2 mg to 10 mg, preferreably from 0.5 mg to 7.5 mg such as of 0.75 mg, 1 mg, 1.25 mg, 1.5 mg, 2. mg, 2.5 mg, 3 mg, 4 mg, or 5 mg.

As discussed above, midodrine may be present as the racemic form or in one of its enantiomeric forms, preferably the therapeutically active enantiomeric form. In those cases where midodrine is present in its therapeutically active enantiomeric form a reduction in the above-mentioned dosage ranges may be relevant.

With respect to the dosage in those cases where desglymidodrine is employed it is envisaged that the same dosages as mentioned above are relevant.

Formulation techniques

In principle any relevant controlled formulation technique for preparing an oral controlled release composition may be applied. Thus, th dosage form may be in the form of a liquid

having e.g. particles dispersed in a dispersion medium or it may be in the form of a single or a multiple unit dosage form intended for use as such as for dispersing in a dispersion medium before use.

In the following is given a short review on general controlled release formulation techniques with an aim of obtaining the type of dissolution profile described above.

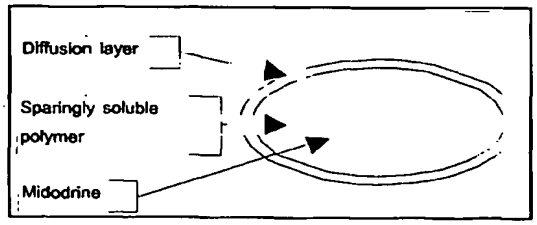
Examples of different controlled release technologies are:

1. Single units
    - 1.1. Coated matrix
    - 1.2 Triple compression
    - 1.3 Multilayer coating

2. Multiple units
    - 2.1 Units having a controlled release coating
    - 2.2 Units having a controlled release matrix
    - 2.3 Units having a controlled release compression coating
    - 2.4 Units with a multilayer coating.

Coated matrix

The idea behind the use of this technology is to coat a sparingly soluble and/or swellable polymer, in which midodrine (or any relevant substance) is embedded, with an insoluble diffusion barrier. The diffusion of midodrine is controlled by the matrix and the coat. This technique will cover the type of dissolution profile described in step 2 above under the heading "Dissolution".



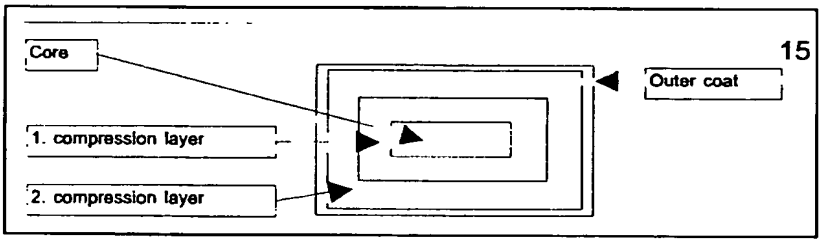
If a soluble outer film layer containing midodrine is applied on the coated matrix, step 1 is achievable too.

Step 3 can be covered by including the technique described below in the triple compression section by having enteric coated units embedded in the matrix.

Triple compression

The basic idea for such a formulation is a core of a polymer with midodrine incorporated. This core is compression coated with a polymer with midodrine incorporated in a lower concentration than in the core. The coated core is compression coated once more with a polymer with midodrine in a higher concentration as in the first coat. Finally, the triple compression unit is spray coated and midodrine is incorporated in the coat. However, the concentrations of midodrine in the different coats may vary markedly.

The idea with the multiple layers is that when the midodrine of the first layer has been almost depleted, the next layer takes over and straightens out the release profile. The spray coating with midodrine gives an immediate burst of the active compound.




Steps 1, 2 and 3 can be covered by use of this technique.

Multilayer coating

The idea with this type of formulation is to coat an inert core with several layers of diffusion barriers, each barrier containing different concentrations of midodrine. The concentration should be highest in the inner coat and lowest in the outer coat. The purpose of the concentration gradient is to compensate for the increasing diffusion distance closer to the core. If the thickness of the diffusion barriers and the concentration gradients are correctly adjusted, steps 1, 2 and 3 will be obtainable.

Use of enteric coating

The correct start of step 3 in the triple compression and multilayer technologies might be optimized by the use of an enteric polymer.

Use of amylose as colon degradable excipient

The correct start of step 3 in the triple compression and multilayer technologies might be optimized by the use of an amylose containing film coating such as a coating containing ethylcellulose and amylose or Eudragit RS and amylose.

Multiple unit systems

The units comprise pellets, granules, crystals, mini tablets or mixtures thereof.

Step 1 can be covered by an uncoated unit.

Step 2 can be covered by the application of a controlled release coating or by formulating the unit as a matrix or a coated matrix.

Step 3 can be covered by the use of an enteric polymer or by having units compression as describe in the triple compression technology.

In specific embodiments, a controlled composition according to the kit of the invention is in the form of a solid dosage form.such as, e.g., tablets, capsules, sachets, solid dispersion, crystals, granules and the like.

A controlled release composition of the kit according to the invention can also comprise at least two parts such as at least a first and a second part, each part contains midodrine and/or, if present, desglymidodrine and the first part being adapted to release midodrine and/or, if present, desglymidodrine, in a controlled manner during the first 0-14 such as, e.g. 0-11 hours after oral intake and the second part being adapted to release midodrine and/or, if present, desglymidodrine, starting at least 6 hours after oral intake.

In such a controlled release composition at least one of the at least two parts is present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitablets.

The two parts of the at least two parts may also be present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitablets, and the two parts may be in admixture.

A controlled release composition according to the kit of the invention may also be in multiple unit dosage form such as, e.g., wherein at least one of the at least two parts comprisies at least two different types of pellets, the first type of pellets corresponding to a first fraction and the second type of pellets corresponding to a second fraction.

Moreover, the at least two parts of the controlled release composition may comprise at least two different types of pellets, the first type of pellets corresponding to the first part and the second type of pellets corresponding to the second part.

A controlled release composition according to the kit of the invention may also as individual units contain minitablets, i.e. be in the form of a multiple unit dosage form comprising at least two different types of minitablets, the first type of minitablets corresponding to the first part and the second type of minitablets corresponding to the second part. In the present context a minitablet is a tablet having a size in a range corresponding to from about 0.7 mm to about 7 mm such as, e.g., in a range corresponding to from about 1 to about 7 mm, from about 1.5 to about 6 mm, from about 2 mm to about 5 mm, from about 2 mm to about 4 mm such as in a range corresponding to from about 2 to about 3 mm.

A controlled release composition according to the kit of the invention may also comprise individual units containing relatively large crystals of the active drug substance. In such cases, the size of the unit is at the most about 1 mm such as, e.g., in a range corresponding to from about 0.1 to about 1 mm, from about 0.2 mm to about 0.8 mm, from about 0.2 mm to about 0.7 mm or from about 0.3 mm to about 0.7 mm.

A controlled release composition according to the kit of the invention may be in the form of a multiple unit dosage form, wherein the first or the second part is in the form of minitablets, in the form of pellets or in the form of large crystals of the active drug substance.

Moreover, at least two fractions may be present in one tablet such as, e.g. a multilayer tablet and the at least first and the second part are each comprised in a layer in the tablet.

Furthermore, a composition according to the kit of the invention may comprise a third part adapted to release midodrine and, if present, desglymidodrine relatively fast from the composition and/or a fourth part adapted to release midodrine and/or desglymidodrine from the composiiton 6-10 hours after oral intake. In one embodiment the third and/or, if present, the fourth part comprise pellets or minitablets or are a layer in a tablet.

With respect to release kinetics, a controlled release composition according to the kit of the invention may have a first part, a second part, a third part and/or a fourth part which have a release kinetic corresponding to a zero or a first order release or a mixture of zero and first order release.

Pharmaceutically acceptable excipients

Apart from the active drug substance in the composition, a pharmaceutical composition according to the kit of the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical composition which has acceptable technical properties.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate,

calcium hydrogen phosphate), calcium sulfate, calcium carbonate, gelatine, polyvinylpyrrolidone (30, 90, Kollidon VA 64), and sodium carboxymethylcellulose. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

Glidants and lubricants may be incorporated such as stearic acid, metallic stearates, talc, waxes and glycerides with high melting temperatures, colloidal silica, sodium stearyl fumarate, polyethylenglycols and alkyl sulphates.

Surfactants may be employed such as non-ionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g., benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, pH adjusting agents, solubilizing agents, wetting agents and buffering agents.

Modified release coating

A unit comprised in a composition according to the invention may be coated with a modified release coating.

The modified release coating is a substantially water-insoluble but water-diffusible coating.

The modified release coating may be applied on the multiple units or on the single units from a solution and/or suspension preferably in an aqueous solvent, but an organic coating composition may also be applied.

Examples of matrix-forming agents are hydroxypropylmethylcellulose, hydroxypropylcellulose, micronised ethylcellulose, low-substituted hydroxypropylcellulose (LH 20, 21, 31).

Examples of film-forming agents which are suitable for use in accordance with the present invention are agents selected from the group consisting of cellulose derivatives such as, e.g., ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate; acrylic polymers such as, e.g., polymethyl methacrylate; vinyl polymers such as, e.g., polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer, vinyl chloride-propylene-vinyl acetate copolymer; silicon polymers such as, e.g., ladder polymer of sesquiphenyl siloxane, and colloidal silica; polycarbonate; polystyrene; polyester; coumarone-indene polymer; polybutadiene; and other high molecular synthetic polymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one preferred embodiment, the acrylic coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL 30 D and Eudragit® RS 30 D, respectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL 30 D and 1:40 in Eudragit® RS 30 D. Eudragit® RL/RS mixtures are insoluble in water

and in digestiv fluids. However, coatings formed from th same are swellable and permeable in aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions may be mixed together in any desired ratio in order to ultimately obtain a modified release formulation having a desirable dissolution profile. The most desirable modified release formulations may be obtained from a retardant coating based on Eudragit® NE 30D, which is a neutral resin having a molecular weight of 800,000.

Examples of enteric polymers are cellulose acetate phthalate, cellulose acetate trimellitate, hydroxy propyl methyl cellulose acetate phthalate, hydroxy propyl methyl cellulose acetate succinate, carboxy methyl ethyl cellulose, polyvinyl acetate phthalate, copolymer of vinyl acetate and crotonic acid and poly(methacrylic acid, ethacrylate).

The amount of coating applied is adapted so as to obtain a predetermined dissolution characteristic of the composition.

However, the amount of coating applied should also be adapted so that there will be no rupturing problems.

The coating may be admixed with various excipients such as plasticizers, anti-adhesives such as, e.g., colloidal silicium dioxide, inert fillers, and pigments in a manner known *per se*.

Tackiness of the water-dispersible film-forming substances may be overcome by simply incorporating an anti-adhesive in the coating. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive or mixture of anti-adhesives is preferably incorporated in the coating in an amount of about 0.1-70% by weight, in particular about 1-60% by weight, and preferably about 8-50% by weight of the film layer. By selecting a small particle size of the talc, a larger surface area is obtained; the

consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of specific anti-adhesives.

The units may further comprise an outer film layer.

In one aspect, the outer second layer comprises a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, the water-based film-forming agent being anti-adhesive at temperatures above about 40 °C, especially temperatures above about 50 °C, such as a temperature between about 60 °C and about 120 °C, and being selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, celluloseacetatephthalate, polyvinyl-acetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

Examples of plasticizers for use in accordance with the present invention include triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl tributyl citrate, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylmaleate, diethylfumarate, diethylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacetate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol, 1,2-propyleneglycol, dibutylsebacate, diethylsebacate and mixtures thereof. The plasticizer is normally incorporated in an amount of less than 10% by weight, calculated on the dry matter content of the coating composition.

The fast onset formulation according to the kit of the invention may be any formulation well known in the art to provide a relative fast release.

With respect to nasal vehicles, polyethyleneglycols is especially preferred such as more n-ethylene glycols represented by the formula II;

$$H(OCH_2CH_2)_pOH \qquad II$$

wherein p is an integer in the range of 1 to 14, including PEG 200 and PEG 300. The polyethyleneglycols may be used in combination with glycufurols. The latter may also be used separately.

The volume of a nasal dosage is preferably within 1000 µl such as within 300 µl, preferable about 150 µl.

The invention is further illustrated in the drawing, wherein

fig. 1 shows the estimated plasma concentration of midodrine,
fig. 2 shows the estimated plasma concentration of desglymidodrine,
fig. 3 shows the estimated *in vivo* dissolution of midodrine,
fig. 4 shows the estimated *in vivo* dissolution of desglymidodrine,
fig. 5 shows the estimated *in vitro* target for dissolution of midodrine and the estimated release rate,
figs. 6-9 illustrate the results of Example 1,
figs. 10-13 illustrate the result of Example 2,
figs. 14-16 illustrate the result of Example 3.

The following examples are intended to illustrate specific embodiments of the controlled release and fast onset formulaion of the kit of present invention but are not intended in any way to limit the invention. Some of the examples are included in order to illustrate that the release rate and dissolution characteristics of a controlled release composition can be changed by varying a number of formulation parameters.

**EXAMPLES**

**Example 1**

**Composition made by employment of triple compression**

A tablet was prepared from the following ingredients:

Core:

| | |
|---|---|
| Midodrine hydrochloride | 5.0 mg |
| Klucel MF | 2.0 mg |
| Methocel E 50 | 93.0 mg |

1st compression layer:

| | |
|---|---|
| Midodrine hydrochloride | 1.5 mg |
| Klucel MF | 6.6 mg |
| Methocel E 15 | 156.9 mg |

2nd compression layer:

| | |
|---|---|
| Midodrine hydrochloride | 2.8 mg |
| Methocel E 50 | 247.2 mg |

Using the core composition a core weighing 100 mg was compressed using a punch 6 mm in diameter. The core was compression coated using 165 mg of the 1st compression layer composition and a punch of 9 mm in diameter. The thus compression coated core was compression coated again using 250 mg of the 2nd compression layer composition and a punch of 11 mm in diameter.

A composition comprising midodrine hydrochloride 1.2 mg, Methocel E5 9.7 mg and Talc 8.5 mg was applied to the tablet by spray coating.

The following results were obtained with respect to dissolution and release rate (the dissolution method employed throughout the examples and claims is in accordance with the method described in USP and Ph.Eur. method 2 (paddle) employing 0.1 N hydrochloric acid as dissolution medium, 500 ml of dissolution medium, 100 rpm, 37°C and the amount of midodrine (and/or desglymidodrine) released was measured by UV at at wavelength of 213.4.

| | % w/w dissolved based on the total weight of the composition tested | | | |
|---|---|---|---|---|
| time | core | core | core | core |

| (hours) | | + 1 layer | + 2 layers | + 2 layers and coated |
|---|---|---|---|---|
| 0,5 | 14,86 | 4.02 | | 13.30 |
| 1 | | 5.90 | 5.89 | 15.89 |
| 2 | 26.26 | 9.38 | 9.06 | 20.15 |
| 3 | 32.10 | 14.94 | 11.68 | 23.75 |
| 4 | 36.24 | 25.59 | 13.83 | 27.12 |
| 6 | 42.48 | 44.47 | 17.91 | 36.23 |
| 8 | 45.02 | 56.66 | 21.93 | 52.70 |
| 10 | | 63.07 | 33.67 | 70.52 |
| 12 | | | 40.17 | 85.40 |
| 15 | | | 56.02 | 95.67 |
| 18 | | | 76.08 | 96.81 |
| 20 | | | 82.46 | |

The dissolution profiles of the compositions tested are illustrated in Figs. 6-9 together with the release rate (% w/w dissolved/hour).

**Example 2**

**Composition made as a coated matrix**

The following compositions were prepared:

| | | |
|---|---|---|
| Composition 1: | <u>Core:</u> | |
| | Midodrine hydrochloride | 10.0 mg |
| | Klucel LF | 340.0 mg |
| | <u>Insoluble inner coat</u> | |
| | Methocel E 5 | 0.2 mg |
| | Magnesium stearate | 0.1 mg |
| | Talc Ponderax | 0.4 mg |
| | Anti foam | 4.8 µg |
| | Eudragit NE 30 D | 4.5 mg |

| | | |
|---|---|---|
| | Soluble outer coat | |
| | Methocel E 5 | 1.8 mg |
| | Talc Ponderax | 1.8 mg |
| Composition 2: | Core: | |
| | Midodrine hydrochloride | 10.0 mg |
| | Klucel MF | 340.0 mg |
| | Insoluble inner coat | |
| | Methocel E 5 | 0.2 mg |
| | Magnesium stearate | 0.1 mg |
| | Talc Ponderax | 0.4 mg |
| | Anti foam | 4.8 µg |
| | Eudragit NE 30 D | 4.5 mg |
| | Soluble outer coat | |
| | Methocel E 5 | 1.8 mg |
| | Talc ponderax | 1.8 mg |

Cores of both composition 1 and composition 2 were compressed using a punch 10 mm in diameter. Core weighing 350 mg.

Both types of cores were coated with an insoluble inner coat and a soluble outercout. The release profile can be shifted up or down by changing the amount of weight increase of cores when applying the inner coat.

If suitable, the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers. Furthermore, the release profile can be changed by using other types of matrix former such as acrylic resins, other types of cellulose ethers such as L-HPC (low-substituted hydroxypropylcellulose), HPC (hydroxypropylcellulose), HPMC (hydroxypropylmethylcellulose), HEC (hydroxyethylcellulose), MC (methylcellulose), HEMC (hydroxyethylmethylcellulose), EC (ethylcellulose) or other viscosity grades of HPC (hydroxypropylcellulose).

The following results were obtained with respect to dissolution and release rate (perfomed in accordance with the method described herein):

| time (hours) | % w/w dissolved based on the total weight of the composition tested | | | |
|---|---|---|---|---|
| | comp. 1 | comp. 1 coated | comp. 2 | comp. 2 coated |
| 1 | 16.72 | 7.67 | 15.77 | 6.41 |
| 2 | 27.25 | 14.60 | 22.36 | 10.85 |
| 3 | 36.86 | 21.24 | | |
| 4 | 45.66 | 27.59 | 32.14 | 19.62 |
| 6 | 60.37 | 38.18 | 36.26* | 24.03* |
| 8 | | 49.10 | 49.13* | 38.74* |
| 10 | 80.74 | 59.82 | | |
| 12 | 87.09 | 69.74 | 54.44* | 44.83* |
| 15 | 91.37 | 81.48 | 63.06 | 54.89 |
| 18 | | | 66.70* | 59.27* |

* Time is 5, 9, 11 and 17 hours

**Example 3**

**Multilayer coating compositions**

The following compositions were prepared:

| | | |
|---|---|---|
| Composition 1: | Core (Non pareil) | 200 mg |
| | <u>1. coat</u> | |
| | Midodrine | 4.0 mg |
| | Methocel E 5 M | 0.3 mg |
| | Magnesium Stearate | 60.0 µg |

| | |
|---|---|
| Talc ponderax | 0.5 mg |
| Anti foam | 4.0 µg |
| Eudragit NE 30 D | 5.2 mg |

2. coat

| | |
|---|---|
| Midodrine | 3.0 mg |
| Methocel E 5 M | 0.3 mg |
| Magnesium Stearate | 60.0 µg |
| Talc ponderax | 0.5 mg |
| Anti foam | 4.0 µg |
| Eudragit NE 30 D | 6.1 mg |

3. coat

| | |
|---|---|
| Midodrine | 2.0 mg |
| Methocel E 5 M | 0.3 mg |
| Magnesium Stearate | 80.0 µg |
| Talc ponderax | 0.6 mg |
| Anti foam | 6.0 µg |
| Eudragit NE 30 D | 7.1 mg |

4. coat

| | |
|---|---|
| Midodrine | 1.0 mg |
| Methocel E 5 M | 0.4 mg |
| Magnesium Stearate | 80.0 µg |
| Talc ponderax | 0.7 mg |
| Anti foam | 6.0 µg |
| Eudragit NE 30 D | 7.8 mg |

Outer coat

| | |
|---|---|
| Methocel E 5 | 1.0 mg |
| Talc ponderax | 1.0 mg |

Non-pareil beads were coated in four steps with four different film in a fluid bed coater.

1. film comprising 1. coat
2. film comprising 2. coat
3. film comprising 3. coat
4. film comprising 4. coat.

A final layer of coating comprising Outer coat was applied and the films were cured at 70°C

| | | |
|---|---|---|
| Composition 2: | Core (Non pareil) | 200 mg |

Non-pareil beads were coated in seven steps with four different films alternating with a blank film in a fluid bed coater.

The four different film formulations are similar to the four different film formulations in composition 1, the alternating coats are as follows:

| | Alternating coat | |
|---|---|---|
| | Methocel E 5 M | 0.2 mg |
| | Magnesium stearate | 40.0 µg |
| | Talc ponderax | 0.3 mg |
| | Anti foam | 2.0 µg |
| | Eudragit NE 30 D | 3.5 mg |

1. film comprising 1. coat
2. film comprising Alternating coat
3. film comprising 2. coat
4. film comprising Alternating coat
5. film comprising 3. coat
6. film comprising Alternating coat
7. film comprising 4. coat

A final layer of coating comprising Outer coat in composiiton 1 was applied and the films

were cured at 70°C.

| | | |
|---|---|---|
| Composition 3: | Core (Non pareil) | 200 mg |
| | 1. coat | |
| | Midodrine | 4.0 mg |
| | Paraffin, solid | 0,3 mg |
| | Acetyltributyl citrate | 0.1 mg |
| | Ethylcellulose | 1.9 mg |
| | Aerosil 200 | 28.0 µg |
| | 2. coat | |
| | Midodrine | 3.0 mg |
| | Paraffin, solid | 0,3 mg |
| | Acetyltributyl citrate | 0.1 mg |
| | Ethylcellulose | 2.2 mg |
| | Aerosil 200 | 32.0 µg |
| | 3. coat | |
| | Midodrine | 2.0 mg |
| | Paraffin, solid | 0,4 mg |
| | Acetyltributyl citrate | 0.1 mg |
| | Ethylcellulose | 2.5 mg |
| | Aerosil 200 | 40.0 µg |
| | 4. coat | |
| | Midodrine | 1.0 mg |
| | Paraffin, solid | 0,4 mg |
| | Acetyltributyl citrate | 0.2 mg |
| | Ethylcellulose | 2.8 mg |
| | Aerosil 200 | 40.0 µg |

Outer coats

| | |
|---|---|
| Paraffin, solid | 0,5 mg |
| Acetyltributyl citrate | 0.2 mg |
| Ethylcellulose | 3.3 mg |
| Aerosil 200 | 50.0 µg |

Non-pareil beads were coated in four steps with four different films in a fluid bed coater:

1. film comprising 1. coat
2. film comprising 2. coat
3. film comprising 3. coat
4. film comprising 4. coat.

A final layer of coating comprising Outer coats was applied.

The following results were obtained with respect to dissolution and release rate (perfomed in accordance with the method described herein):

% w/w dissolved based on the total weight of the composition tested

| time (hours) | composition 1 | composition 2 | composition 3 |
|---|---|---|---|
| 0,5 | 26.02 | 19.84 | 5.41 |
| 1 | 55.24 | 33.08 | |
| 2 | 78.38 | 64.39 | 22.92 |
| 3 | 85.01 | 77.64 | 35.52 |
| 4 | 87.91 | 83.41 | 43.61 |
| 6 | 90.43 | 88.39 | 55.16 |
| 8 | 91.61 | 90.63 | 61.75 |
| 15 | | | 72.09 |

If suitable, the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

**Example 4**

**Preparation of a controlled release composition using commercially available filmforming agents**

The present example illustrates the preparation of a coated pellet composition. The aim was to prepare pellets having a release kinetic different from zero order release.

Pellets were prepared from the following ingredients:

| | | |
|---|---|---|
| I | Midodrine hydrochloride | 600.0 g |
| II | Microcrystalline cellulose (Type PH 101) | 752.0 g |
| III | Lactose monohydrate | 2608.0 g |
| IV | Sodium carboxymethylcellulose | 40.0 g |
| V | Purified water | 1120.0 g |

I + II + III + IV are admixed in a Fielder intensive mixer at an appropiate time and mixing intensity.

V is applied to the mixture (I-IV) while mixing. When V is applied the mixing is continued at an appropiate time with an appropiate mixing intensity.

The wetted mass is extruded through a screen with apertures between 0.4 -1.0 mm.

The extrudate is spheronised until the surface of the resulting pellets is smooth.

An inner and an outer coating were applied:

Inner coat

The weight of the pellets is increased with 8.5% w/w.

| | | |
|---|---|---|
| I | Hydroxypropylmethylcellulose | 13.5 g |
| II | Magnesium stearate | 2.9 g |
| II | Talc | 25.2 g |
| IV | Eudragit NE 30 D | 895.1 g |
| V | Purified water | 1135.4 g |

The pellets are coated in a fluid bed with appropriate process parameters.

Immediately after the inner coat has been applied an outer coat is applied.

Outer coat

The weight of the pellets is increased with 1% w/w.

| | | |
|---|---|---|
| I | Hydroxypropylmethylcellulose | 20.0 g |
| II | Talc | 20.0 g |
| III | Purified water | 460.0 g |

The pellets are coated in a fluid bed with appropriate process parameters.

The weight of 1 unit dose containing 30 mg midodrine hydrochloride is 219 mg.

The release profile can be shifted up or down by changing the amount of weight increase of pellets when applying the inner coat.

The release profile can be changed by mixing fractions of pellets with different amounts of inner coating applied or the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

Furthermore, the release profile can be changed by applying an enteric coating to a fraction of coated pellets.

**Example 5**

**Preparation of a controlled release formulation using a film containing paraffin**

The present example illustrates the preparation of a coated pellet composition. The aim was to prepare pellets having a release kinetic different from zero order release.

Coated pellets were prepared from the following ingredients:

The composition and manufacturing process of pellets are similar to example 6.

A coating was applied. Paraffin-containing film; the weight of the pellets is increased with 6% w/w.

| | | |
|---|---|---|
| I | Paraffin, solid | 29.89 g |
| II | Acetyltributyl citrate | 10.53 g |
| III | Ethyl cellulose | 196.61 g |
| IV | Silicium dioxide (Aerosol 200) | 2.95 g |
| V | Isopropyl alcohol | 3970.03 g |

The pellets are coated in a fluid bed with appropriate process parameters.

The weight of 1 unit dose containing 30 mg midodrine hydrochloride is 212 mg.

**Example 6**

**Preparation of a controlled release composition having a zero order release**

The present example illustrates the preparation of a coated beads composition. The aim was to prepare beads having a zero order release kinetic.

Coated beads were prepared from the following ingredients:

Non dissolvable non-pareil beads of equal size are coated with a suspension of midodrine hydrochloride. A diffusion barrier is coated on top of the midodrine hydrochloride layer, and thereby controlling the release of midodrine hydrochloride.

4000 g non-pareil beads having a uniform particle size in a range between 0.4 mm and 1.0 mm are transferred to a fluid bed coater.

The beads are coated with coating suspension 1 (containing midodrine hydrochloride):

| | | |
|---|---|---|
| I | Hydroxypropylmethylcellulose | 8.8 g |
| II | Magnesium stearate | 1.9 g |
| III | Talc | 16.5 g |
| IV | Eudragit NE 30 D | 585.1 g |
| V | Purified water | 742.1 g |
| VI | Midodrine hydrochloride | 200.0 g |

The weight of the beads is increased with 10% w/w.

The beads are coated employing appropriate process parameters.

Immediately after coating suspension 1 has been applied a second coating suspension is applied.

The beads are coated with coating suspension 2:

| | | | |
|---|---|---|---|
| | I | Hydroxypropylmethylcellulose | 11.7 g |
| | II | Magnesium stearate | 2.5 g |
| | III | Talc | 21.7 g |
| | IV | Eudragit NE 30 D | 772.3 g |
| | V | Purified water | 979.6 g |

The weight of the coated beads is increased with 6% w/w.

The pellets are coated employing appropriate process parameters.

Immediately after coating suspension 2 has been applied a third coating suspension is applied.

The beads are coated with coating solution 3:

| | | | |
|---|---|---|---|
| | I | Hydroxypropylmethylcellulose | 23.3 g |
| | II | Talc | 23.3 g |
| | III | Purified water | 536.8 g |

The weight of the coated beads is increased with1% w/w.

The beads are coated in a fluid bed employing appropriate process parameters.

The weight of 1 unit dose containing 20 mg midodrine hydrochloride is 471 mg.

By changing the weight gain of the beads when applying the second coating suspension, the release profile can be shifted up or down.

The release profile can be changed by mixing fractions of beads having different amounts of second coating suspension applied or the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations

thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

The above mentioned filmforming agents can also be combined with pore forming agents such as cellulose ethers, polyoles, PEG´s.
Furthermore, the release profile can be changed by applying an enteric coating to a fraction of the coated beads.

**Example 7**

**Preparation of a zero order controlled release composition**

The present example illustrates the preparation of a coated minitablet composition. The aim was to prepare coated minitablets of equal size in order to obtain a zero order release kinetic.

Formulation of minitablets:

| | | |
|---|---|---|
| I | Midodrine hydrochloride | 800.0 g |
| II | Dicalcium phosphate | 2960.0 g |
| III | Talc | 100.0 g |
| IV | Magnesium stearate | 40.0 g |
| V | Polyvinylpyrrolidone 90 | 100.0 g |
| VI | Purified water | 800.0 g |

V is dissolved in VI.

I + II are transferred to a Fielder intensive mixer and admixed at an appropiate time and mixing intensity.

The mixture is wetted with the solution V + VI.

Granulation is performed at an appropriate time and mixing intensity.

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

The dried granulate is passed through a suitable sieve. IV + V are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

A dose of 30 mg midodrine corresponds to 10 minitablets.

Coating of the minitablets:

The minitablets are coated with inner and outer coatings corresponding to the description in Example 6.

By changing the weight gain of the minitablets when applying the inner coat, the release profile can be shifted up or down

The release profile can be changed by mixing fractions of minitablets having different amounts of inner coating applied or the release profile can be changed by coating with other acrylic resin such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers.

The above mentioned filmforming agents can also be combined with pore forming agents such as, e.g., cellulose ethers, polyoles, PEG´s, etc.

Furthermore, the release profile can be changed by applying an anteric coating to a fraction of the coated minitablets.

**Example 8**

**Preparation of a controlled release composition having a release kinetic different from that of zero order**

Matrix minitablets:

| | | |
|---|---|---|
| I | Midodrine hydrochloride | 800.0 g |
| II | Ethyl cellulose (10 µm) | 2960.0 g |
| III | Talc | 200.0 g |
| IV | Magnesium stearate | 40.0 g |
| V | Purified water | 800.0 g |

I + II are admixed in a Fielder intensive mixer at an appropriate time and mixing intensity.

The mixture is wetted with V while mixing at an appropriate mixing intensity.

The wetted mixture is granulated at an appropriate time and mixing intensity.

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

The dried granulate is passed through a suitable sieve. III + IV are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

A dose of 30 mg of midodrine hydrochloride is contained in 10 minitablets.

If suitable, the release profile can be changed by using other cellulose ethers such as HPC, L-HPC, HPMC or combinations of thereof.

The principle of a matrix composition may also be used for a single unit tablet containing the total amount of midodrine hydrochloride in one unit.

In order to further increase the retardation of the dissolution of midodrine hydrochloride the minitablets may be coated according to example 6. The amount of coating applied may be varied to shift the dissolution profile up or down.

**Example 9**

**Preparation of a controlled release composition having release kinetic different form zero order**

Matrix minitablets:

| | | |
|---|---|---|
| I | Midodrine hydrochloride | 800.0 g |
| II | Ethyl cellulose (10 µm) | 2960.0 g |
| III | Talc | 200.0 g |
| IV | Magnesium stearate | 40.0 g |
| V | Isopropyl alcohol | 800.0 g |

I + II are admixed in a Fielder intensive mixer at an appropriate time and mixing intensity.

The mixture is wetted with V while mixing at an appropriate mixing intensity.

The wetted mixture is granulated for an appropriate time and mixing intensity.

The drying of the wet granulate is carried out in an Aeromatic fluid bed.

The dried granulate is passed through a suitable sieve. III + IV are sieved through a 0.3 mm sieve and admixed to the sieved particulate mixture in a cube mixer for 10 min.

The thus obtained particulate mixture is compressed into tablets weighing 15 mg.

A dose of 30 mg of midodrine hydrochloride is contained in 10 minitablets

In order to further increase the retardation of the dissolution of midodrine hydrochloride the minitablets may be coated according to example 6. The amount of coating applied may be varied to shift the dissolution profile up or down.

**Exampl 10**

**Preparation of a controlled r leas composition having rel as kinetic different form zero order**

The present example illustrates the preparation of a two layer tablet.

Two layer tablets (matrix tablets):

The tablet is composed of two different layers of matrices, each layer having it's own release profile. The two layer tablet may be coated according to example 6 in order to further retard the release profile.

Layer 1:

| | | |
|---|---|---|
| I | Midodrine Hydrochloride | 200 g |
| II | Klucel MF | 40 g |
| III | Methocel E 50 | 1700 g |
| IV | Talc | 50 g |
| V | Magnesium stearate | 10 g |
| VI | Purified water | 400 g |

I + II + III are mixed and granulated with VI.

The wet granulate is dried. The dry granulate is passed through a 1 mm sieve, and IV + V are admixed to the particulate mixture.

Layer 2:

| | | |
|---|---|---|
| I | Midodrine Hydrochloride | 100 g |
| II | Klucel MF | 20 g |
| III | Methocel K 15 | 850 g |
| IV | Talc | 25 g |
| V | Magnesium stearate | 5 g |
| VI | Purified water | 200 g |

I + II + III are mixed and granulated with VI.

The wet granulate is dried. The dry granulate is passed through a 1 mm sieve, and IV + V are admixed to the particulate mixture.

200 mg granulate of the layer 1 granulate is dosed into a tabletting machine and is compressed. 100 mg granulate of the layer 2 granulate is dosed on top of the first layer, and the two layers are compressed into one tablet.

The release profile may be changed by applying other grades or amounts of the mentioned polymers, by using other cellulose ethers or by using other types of polymers such as acrylic resins.

**Example 11**

**Liquid formulation for Transdermal delivery using Iontophoresis patches**

| | Composition | |
|---|---|---|
| I | Midodrine HCl | 50.0 g |
| II | Sodium edetate | 0.5 g |
| | Disodium hydrogen phosphate dihydrate | 2.0 g |
| | Sodium dihydrogen phosphate dihydrate | 2.0 g |
| III | Water for injection | 900.0 g |
| IV | Water for injection | ad 1000.0 g |

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

The formulation is filtrated (0,22 :m), and filled into a patch-device.

Tonicity agents may be dextrose, glycerol, sorbitol, mannitol, potassium nitrate and sodium sulphate decahydrate or mixtures thereof.

pH may be adjusted to the appropiate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these

**Example 12**

**Powder preparation e.g for use in a needle-free device.**

| | Composition | |
|---|---|---|
| I | Midodrine HCl | 1000.0 g |

The particle size distributions for the ingredients should be appropiate for deposition of the formulation through the skin e.g. 0.5:m to 10:m.

The powder is filled into drug Casette, each containing 5 mg Midodrine HCl.

Suspending agents such as glucose, lactose, celluloses, starches (maize-, rice-, potato-), calcium phosphate or mixtures of these may be used.

**Example 13**

**Liquid formulation using the Intraject® Needle-free device from Weston Medical .**

| | | Composition | |
|---|---|---|---|
| | I | Midodrine HCl | 50.0 g |
| | II | Sodium edetate | 0.5 g |
| | | Disodium hydrogen phosphate dihydrate | 2.0 g |
| | | Sodium dihydrogen phosphate dihydrate | 2.0 g |
| | III | Water for injection | 900.0 g |
| | IV | Water for injection | ad 1000.0 g |

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

The formulation is filtrated (0,22 :m) and is filled into glass devices with a piston ( e.g. teflon) and a stopper (e.g. rubber (natural or synthetic substances))

Tonicity agents may be dextrose, glycerol, sorbitol, mannitol, potassium nitrate and sodium sulphate decahydrate or mixtures thereof.

pH may be adjusted to the appropiate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these.

**Example 14**

**Buccal wafer-like formulation**

| | | Composition | |
|---|---|---|---|
| | I | Midodrine HCl | 25.0 g |
| | II | Hydroxypropylmethylcellulose | 250.0 g |

| | | |
|---|---|---|
| III | Propylene glycol | 50.0 g |
| IV | Purified water | 675.0 g |

A suspension is prepared by thoroughly admixing II to a vehicle composed of III and IV. The mixture is allowed to settle until maximum viscosity is achieved. I is then carefully blended with the mixture II+III+IV to achieve a homogenous formulation.
A process foil is then evenly coated with the formulation in a predefined thickness of typically 40 µm to 200 µm. In a multistage drying process the solvent is allowed to evaporate and the residual water content is adjusted. Finally, the single wafers of about 1-2 $cm^2$ containing a single dose of midodrine are produced by cutting.

Film-forming polymers such as sodium carboxymethyl cellulose, hydroxyethyl cellulose or hydroxypropyl cellulose or mixtures of these may be used.

Excipients may be added as fillers, such as lactose, silicone, silicone derivatives, mineral oil, glycerol and starches (maize-, rice-, potato-) and powdered calcium phosphate or combinations of these.

Disintegration and release can be controlled by excipients such as polyethylene glycol, alcohol, propylene glycol, phospholipids, sorbitan fatty acid esters and derivatives thereof, glycerol fatty acid esters, polyoxyethylene polyol fatty acid esters, polyoxyethylene stearates and polyoxyethylene fatty ethers or mixtures of these.
The organoleptic properties of the formulation may be improved by addition of flavors, coloring agents and/or sweeteners such as sorbitol, mannitol, saccharin, acesulfame, aspartame, cyclamate salts or mixtures of these.

**Example 15**

**Liquid preparations for pulmonal delivery.**

A. Pressurised metered-dose preparation for inhalation

Composition

| | | | |
|---|---|---|---|
| I | Midodrine HCl | 50.0 g |
| II | Norflurane | ad 1000.0 ml |

I is dissolved or suspended in liquid II at low temperature during continuous agitation. For suspensions, the particle size distribution should be appropiate for deposition of the formulation in the lung, e.g. 0.5 μm to 10 μm.

The product is filled into suitable pressurised multi-dose containers delivering 100 μl pr. dose.

Other propellants such as dichlorodifluoromethane, dichlorotetrafluoroethane and trichlorofluoromethane or mixtures of these may be used.

Glidants such as oleic acid and derivatives and isopropyl myristate or mixtures of these may be used to reduce friction during administration.

B. Liquid for nebulisation

Composition

| | | | |
|---|---|---|---|
| I | Midodrine HCl | 2.5 g |
| II | Sodium edetate | 0.5 g |
| | Disodium hydrogen phosphate dihydrate | 2.0 g |
| | Sodium dihydrogen phosphate dihydrate | 2.0 g |
| III | Purified water | 900.0 g |
| IV | Purified water | ad 1000.0 g |

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.

The formulation is filled into 2 ml ampoules or other suitable unit-dose containers.

Excipients may be added to increase the solubility of midodrine, such as polyethylene glycol, alcohol, glycofurol, phospholipids, poloxamer, polyoxyethylene castor oil derivatives, polysorbates, propylene glycol and cyclodextrins or combinations of these. Tonicity agents may be e.g dextrose, glycerol, sorbitol, mannitol, potassium nitrate and sodium sulphate decahydrate or mixtures thereof.
pH may be adjusted to the appropiate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these.
Sufficient microbiological preservation may be achieved by addition of benzalconium chloride or parabenes.
Suitable flavors can be added to the formulation and the taste can be further adjusted by use of sweeteners such as saccharin, acesulfame, aspartame, cyclamate salts or mixtures of these.

**Example 16**

**Powder preparation for pulmonal delivery.**

| | Composition | |
|---|---|---|
| I | Midodrine HCl | 500.0 g |
| II | Glucose | 500.0 g |

The particle size distributions for the ingredients should be appropiate for deposition of the formulation in the lung, e.g. 0.5 μm to 10 μm.
I and II is carefully mixed and sieved. The powder is filled into capsules or other suitable unit-dose containers, each containing 10 mg of the formulation.

Other suspending agents such as lactose, celluloses, starches (maize-, rice-, potato-) calcium phosphate or mixtures of these may be used.

**Exampl 17**

**Nasal formulation.**

| | Composition | |
|---|---|---|
| I | Midodrine HCl | 50.0 g |
| II | Sodium edetate | 0.5 g |
| | Disodium hydrogen phosphate dihydrate | 2.0 g |
| | Sodium dihydrogen phosphate dihydrate | 2.0 g |
| III | Purified water | 900.0 g |
| IV | Purified water | ad 1000.0 g |

I is dissolved in III upon continuous stirring. The remaining solid ingredients (II) are added to the solution one by one during continuous stirring. Following complete dissolution of the solids, purified water is added to a total weight of 1000.0 g.
The formulation is filled into appropiate nasal spray devices delivering 100 µl pr. dose.

Excipients may be added to increase the solubility of midodrine, such as polyethylene glycol, alcohol, glycofurol, phospholipids, poloxamers, polyoxyethylene castor oil derivatives, polysorbates, propylene glycol and cyclodextrins or combinations of these.
Tonicity agents may be dextrose, glycerol, sorbitol, mannitol, potassium nitrate and sodium sulphate decahydrate or mixtures thereof.
pH may be adjusted to the appropiate value by use of additional buffer salts such as citric acid, sodium citrate, and potassium dihydrogen phosphate or mixtures of these.
Sufficient microbiological preservation may be achieved by addition of benzalconium chloride or parabenes.

**A. Dissolution method used for Midodrine Quick Release Tablets:**

- Buccal tablets, granulation
- Buccal tablets, direct compression

Apparatus:
Dissolution apparatus 4, according to USP and Ph. Eur.
Flow-through cell
Flow rate: 2-8 ml/min.
Temperature: 37°C
Dissolution medium: isotonic buffer pH 6.8
UV-detection: 213.4 nm (Isospectric wavelength for Midodrine HCl and metabolite ST 1059)

Samples are withdrawn regularly for up to 30 minutes in order to present a suitable dissolution profile. Absorbances of the samples are measured by direct UV-measurement. Quantification is based on response factors calculated on standard solutions.

**B. Dissolution method used for Midodrine Quick Release Tablets:**

- Melt tablets
- Quick release tablets for per oral ingestion

Apparatus:
Dissolution apparatus 2, according to USP and Ph. Eur.
Paddle method
Rotations: 100 rpm
Temperature: 37°C
Dissolution medium: purified water
Volume: 500 ml
UV-detection: 213.4 nm (Isospectric wavelength for Midodrine HCl and metabolite ST 1059)

Samples are withdrawn regularly for up to 30 minutes in order to present a suitable dissolution profile. Absorbances of the samples are measured by direct UV-measurement. Quantification is based on response factors calculated on standard solutions.

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## CLAIMS

1. A pharmaceutical kit comprising a controlled release pharmaceutical composition for oral use comprising midodrine or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the composition being adapted to release midodrine and/or desglymidodrine in such a manner that a relatively fast peak plasma concentration of desglymidodrine is obtained and that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 9 hours such as, e.g. at least about 10 hours, at least about 11 hours., at least about 12 hours, at least about 13 hours, at least about 14 hours or about 14 hours;
and one or more fast onset formulations of midodrine or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the fast onset formulation being adapted to provide midodrine and/or desglymidodrine in such a manner that a relatively fast peak plasma concentration of desglymidodrine is obtained upon administration of the fast onset formulation.

2. A pharmaceutical kit according to claim 1, wherein the controlled release pharmaceutical composition provides the relatively fast peak plasma concentration of midodrine and/or desglymidodrine within about
15 min - 3 hours such as, e.g. about 0.5-1.5 hours or about 1 hour after oral administration.

3. A pharmaceutical kit according to claim 1, wherein the plasma concentration of desglymidodrine from the controlled release formulation is maintained at a therapeutically active level for about 6-16 hours such as, e.g. about 7-16, about 8-15, about 9-15, about 10-15, about 11-14, about 12-14 or about 13-13, or for at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours or at least about 14 hours.

4. A pharmaceutical kit according to claim 1, wherein the plasma concentration of desglymidodrine from the controlled release formulation is maintained at a relatively constant level for about 6-14 hours such as, e.g. for at least about 6 hours, at least about

7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours or at least about 12 hours.

5. A pharmaceutical kit according to claim 4, wherein the relatively constant level is n ± 40% and wherein n is the plasma concentration in ng/ml and monitored in healthy persons.

6. A pharmaceutical kit according to claim 1 containing midodrine or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical kit according to claim 6, wherein a peak plasma concentration of midodrine from the controlled release composition and/or from the fast onset formulation is obtained 15-90 min after oral administration.

8. A pharmaceutical kit according to claim 6, wherein the plasma concentration of midodrine after oral administration of the controlled release formulation is maintained at a relatively constant level for about 5-11 hours such as, e.g. at least about 6 hours, at least about 7 hours or at least about 8 hours.

9. A pharmaceutical kit according to claim 8, wherein the relatively constant level is m ± 40% and wherein m is the plasma concentration in ng/ml and monitored in healthy persons.

10. A pharmaceutical kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - is:

1-15% w/w is released from the controlled release composition within the first 30 min after start of the test,
10-30% (25%) w/w is released about 30 min after start of the test,
15-40% (35%) w/w is released about 1 hour after start of the test
20-45% (39%) w/w is released about 2 hours after start of the test,
20-55% (47%) w/w is released about 3 hours after start of the test,
25-65% (53%) w/w is released about 4 hours after start of the test,

30-75% (66%) w/w is released about 6 hours after start of the test,
45-85% (80%) w/w is released about 8 hours after start of the test,
65-100% (93%) w/w is released about 10 hours after start of the test,
75-100% (100%) w/w is released about 12 hours after start of the test.

11. A pharmaceutical kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - is as follows (±10% w/w of the values stated below):

about 25% w/w is released about 30 min after start of the test,
about 35% w/w is released about 1 hour after start of the test,
about 39% w/w is released about 2 hours after start of the test,
about 47% w/w is released about 3 hours after start of the test,
about 53% w/w is released about 4 hours after start of the test,
about 66% w/w is released about 6 hours after start of the test,
about 80% w/w is released about 8 hours after start of the test,
about 93% w/w is released about 10 hours after start of the test,
about 100% w/w is released about 12 hours after start of the test.

12. A pharmaceutical kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - is:

1-15% w/w is released from the composition within the first 30 min after start of the test,
10-30% (25%) w/w is released about 30 min after start of the test,
15-40% (35%) w/w is released about 1 hour after start of the test,
20-45% (39%) w/w is released about 2 hours after start of the test,
20-55% (47%) w/w is released about 3 hours after start of the test,
25-65% (53%) w/w is released about 4 hours after start of the test,
30-75% (66%) w/w is released about 6 hours after start of the test,
35-85% (75%) w/w is released about 7 hours after start of the test,
45-95% (90%) w/w is released about 8 hours after start of the t st,

65-100% (97%) w/w is released about 10 hours after start of the test,
75-100% (100%) w/w is released about 12 hours after start of the test.

13. A pharmaceutical kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - is:

1-15% w/w is released from the composition within the first 30 min after start of the test,
15-30% (25%) w/w is released about 30 min after start of the test,
20-40% (35%) w/w is released about 1 hour after start of the test,
25-45% (39%) w/w is released about 2 hours after start of the test,
30-55% (47%) w/w is released about 3 hours after start of the test,
40-65% (53%) w/w is released about 4 hours after start of the test,
50-75% (66%) w/w is released about 6 hours after start of the test,
60-85% (75%) w/w is released about 7 hours after start of the test,
70-95% (90%) w/w is released about 8 hours after start of the test,
80-100% (97%) w/w is released about 10 hours after start of the test,
85-100% (100%) w/w is released about 12 hours after start of the test.

14. A pharmaceutical kit according to claim 6, wherein the release pattern of midodrine from the controlled release composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - is as follows (±10% w/w of the values stated below):

about 25% w/w is released about 30 min after start of the test,
about 35% w/w is released about 1 hour after start of the test,
about 39% w/w is released about 2 hours after start of the test,
about 47% w/w is released about 3 hours after start of the test,
about 53% w/w is released about 4 hours after start of the test,
about 66 w/w is released about 6 hours after start of the test,
about 75% w/w is released about 7 hours after start of the test,
about 90% w/w is released about 8 hours after start of the test,
about 97% w/w is r leased about 10 hours after start of the test,

about 100% w/w is released about 12 hours after start of the test.

15. A pharmaceutical kit according to claim 1 containing desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release pattern of desglymidodrine follows the patterns claimed for midodrine in claims 10-14.

16. A pharmaceutical kit according to claim 6, wherein the release rate of midodrine from the controlled composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution medium and a temperature of 37 °C - follows a curve which has a shape corresponding to
i) a first initial release followed by
ii) a steady release, which is followed by
iii) a second rise in release rate and, finally,
iv) a decline in release rate.

17. A pharmaceutical kit according to claim 16, wherein the second rise in release rate from the controlled composition takes place 5-10 hours such as, e.g., about 5-9 hours, about 6-8 hours after start of the dissolution test.

18. A pharmaceutical kit according to claim 17, wherein the second rise in release rate from the controlled composition takes place 6.5-9 hours after start of the dissolution test simulating the time it takes to reach the colon after oral administration.

19. A pharmaceutical kit according to claim 16, wherein the steady release from the controlled composition starts about 1-3 hours after start of the dissolution test.

20. A pharmaceutical kit according to claim 16, wherein the steady release from the controlled composition is maintained for at least 2 hours such as, e.g. at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 7 hours, at least 8 hours such as about 6-8 hours.

21. A pharmaceutical kit according to claim 6, wherein the release rate of midodrine from the controlled composition - when tested *in vitro* employing dissolution apparatus 2 (paddle) according to USP and Ph. Eur, 100 rpm, 0.1 N hydrochloric acid as dissolution

medium and a temperature of 37 °C - in %/hour is as follows (±10-40%such as, e.g. ±10-30% or ± 10%, ± 15% or ± 20% of the values stated below):

about 35 %/hour about 30 min after start of the test (range e.g. 20-40 %/hour),
about 12 %/hour about 1 hour after start of the test (range e.g 4-15 %/hour),
about 6 %/hour about 2 hours after start of the test (range e.g. 2-10 %/hour),
about 7 %/hour about 3 hours after start of the test (range e.g. 2-10 %/hour),
about 6.5 %/hour about 4 hours after start of the test (range e.g. 2-10 %/hour),
about 6.5 %/hour about 5 hours after start of the test (range e.g. 2-10 %/hour),
about 7.5 %/hour about 6 hours after start of the test (range e.g. 2-10 %/hour),
about 12 %/hour about 7 hours after start of the test (range e.g. 5-15 %/hour),
about 10 %/hour about 8 hours after start of the test (range e.g. 5-15 %/hour),
about 3.5 %/hour about 9 hours after start of the test (range e.g. 0-7 %/hour),
about 2 %/hour about 10 hours after start of the test (range e.g. 0-5 %/hour),
about 1 %/hour about 12 hours after start of the test (range e.g. 0-5 %/hour).

22. A pharmaceutical kit according to claim 1 containing desglymidodrine or a pharmaceutically acceptable salt thereof and wherein the release rate of desglymidodrine from the controlled composition follows the patterns claimed for midodrine in claims 16-22.

23. A pharmaceutical kit according to any of the preceding claims for administration of the controlled composition once or twice daily.

24. A pharmaceutical kit according to claim 6, wherein the $W_{50}$ of midodrine in the controlled composition (defined as corresponding to the time the plasma concentration curve is or is above 50% of the $C_{max}$ value) is from about 5 to about 9 hours such as, e.g. from about 6 to about 8 hours such as, e.g. at least about 6 hours.

25. A pharmaceutical kit according to claim 1, wherein the $W_{50}$ of desglymidodrine in the controlled composition (defined as corresponding to the time the plasma concentration curve is or is above 50% of the $C_{max}$ value is from about 5 to about 12 hours such as, e.g. from about 6 to about 11 hours such as, e.g. at least about 8 hours.

26. A pharmaceutical kit according to any of the preceding claims, wherein midodrine in the controlled composition and/or fast onset formulation is present in the form of (±)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (+)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide, (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide or mixtures thereof.

27. A pharmaceutical kit according to any of the preceding claims, wherein midodrine in the controlled composition and/or fast onset formulation is present in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

28. A pharmaceutical kit according to claim 26 or 27, wherein at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of midodrine in the controlled composition and/or fast onset formulation is present in the therapeutically active enantiomeric form.

29. A pharmaceutical kit according to claim 28, wherein the therapeutically active enantiomeric form of midodrine is (-)-2-amino-N-(β-hydroxy-2,5-dimethoxyphenethyl)acetamide or the (R) form of midodrine.

30. A pharmaceutical kit according to claim 1 containing the active metabolite desglymidodrine (ST 1059), wherein desglymidodrine is present in the form of (±)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (± ST 1059), (+)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (+ ST 1059), (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or mixtures thereof.

31. A pharmaceutical kit according to claim 30, wherein desglymidodrine is present in the racemic form (RS), in the enantiomeric form (R), in the enantiomeric form (S) or in mixtures thereof.

32. A pharmaceutical kit according to claim 30 or 31, wherein at least 90% w/w such as, e.g., at least 95% w/w, at least 97% w/w, at least 98% w/w, at least 99% w/w of desglymidodrine is present in the therapeutically active enantiomeric form.

33. A pharmaceutical kit according to claim 32, wherein the therapeutically active enantiom ric form of desglymidodrine is (-)-α-(aminomethyl)-2,5-dimethoxy-benzenemethanol (- ST 1059) or the (R) form of desglymidodrine ((R) ST 1059).

34. A pharmaceutical kit according to any of the preceding claims, wherein midodrine and/or desglymidodrine are present in the form of a pharmaceutically acceptable salt such as a salt formed between midodrine and/or desglymidodrine and an inorganic acid such as e.g., a hydrochoride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a $H_3PO_3$ salt, a $H_3PO_4$ salt, a $H_2SO_3$ salt, a sulfate, a $H_2SO_5$ salt, or a salt formed between midodrine and/or desglymidodrine and an organic acid such as organic acids like e.g. $H_2CO_3$, acetic acid, $C_2H_5COOH$, $C_3H_7COOH$, $C_4H_9COOH$, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

35. A pharmaceutical kit according to any of the preceding claims wherein the controlled composition and/or fast onset formulation is in liquid or semi-liquid form or in a solid dosage form.

36. A pharmaceutical kit according to claim 35 claims wherein the controlled composition is in the form of tablets, capsules, sachets, solid dispersion, crystals and the like.

37. A pharmaceutical kit according to any of the preceding claims wherein the fast onset formulation is in a form suitable for nasal administration.

38. A pharmaceutical kit according to claim 37, wherein the controlled composition comprises at least two parts such as at least a first and a second part, each part contains midodrine and/or, if present, desglymidodrine and the first part being adapted to release midodrine and/or, if present, desglymidodrine, in a controlled manner during the first 0-14 such as, e.g. 0-11 hours or 0-8 hours after oral intake and the second part being adapted to release midodrine and/or, if present, desglymidodrine, starting at least 6 hours after oral intake.

39. A pharmaceutical kit according to claim 38, wherein at least one of the at least two parts is present in the composition in the form of a multiplicity of individual units such as, e.g. pellets or minitablets.

40. A pharmaceutical kit according to claim 38, wherein the two parts of the at least two parts are present in the controlled release composition in the form of a multiplicity of individual units such as, e.g. pellets or minitablets, and the two parts are in admixture.

41. A pharmaceutical kit according to claim 38 in multiple unit dosage form.

42. A pharmaceutical kit according to claim 41 in the form of a multiple unit dosage form, wherein at least one of the at least two parts comprising at least two different types of pellets, the first type of pellets corresponding to a first fraction and the second type of pellets corresponding to a second fraction.

43. A pharmaceutical kit according to claim 41, wherein the at least two parts of the controlled release composition comprise at least two different types of pellets, the first type of pellets corresponding to the first part and the second type of pellets corresponding to the second part.

44. A pharmaceutical kit according to claim 41 in the form of a multiple unit dosage form comprising at least two different types of minitablets, the first type of minitablets corresponding to the first part and the second type of minitablets corresponding to the second part.

45. A pharmaceutical kit according to claim 41 in the form of a multiple unit dosage form, wherein the first or the second part is in the form of minitablets.

46. A pharmaceutical kit according to claim 41, wherein the first or the second part is in the form of pellets.

47. A pharmaceutical kit according to claim 38, wherein the at least two fractions is present in a tablet.

48. A pharmaceutical kit according to claim 47, wherein the tablet is a multilayer tablet and the at least first and the second part are each comprised in a layer in the tablet.

49. A pharmaceutical kit according to claim 38 further comprising a third part adapted to release midodrine and, if present, desglymidodrine relatively fast from the composition.

50. A pharmaceutical kit according to claim 38 further comprising a fourth part adapted to release midodrine and/or desglymidodrine from the composition 6-10 hours after oral intake.

51. A pharmaceutical kit according to claim 38 further comprising a fourth part adapted to release midodrine and/or desglymidodrine from the composition in the colon after oral intake.

52. A pharmaceutical kit according to claim 50 or 51, wherein the third and/or, if present, the fourth part comprise pellets or minitablets or are an layer in a tablet.

53. A pharmaceutical kit according to claim 38, wherein the first part has a release kinetic corresponding to a zero or a first order release, a mixture of zero and first order release, or any other order of release such as, e.g. 1½, third or fourth order release.

54. A pharmaceutical kit according to claim 38 wherein the second part has a release kinetic corresponding to a zero or a first order release, a mixture of zero and first order release, or any other order of release such as, e.g. 1½, third or fourth order release.

55. A pharmaceutical kit according to claim 49, wherein the third fraction has a release kinetic which corresponds to that of a plain release tablet.

56. A pharmaceutical kit according to any of the preceding claims wherein the fast onset formulation results in a peak plasma concentration within 90 minutes such as within 60 minutes prefereable within 45 minutes, more preferred within 30 minutes and still more perferred within 20 minutes upon administration of the fast onset formulation.

57. A pharmaceutical kit according to any of the the preceding claims wherein the fast onset formulation is a nasal formulation.

58. A pharmaceutical kit according to claim 57 wherein the nasal formulation comprises polyethyleneglycol and/or glycofurol as a nasal vehicle.

59. A pharmaceutical kit according to claim 58 wherein the polyethyleneglycol is PEG 200 and/or PEG 300.

60. A pharmaceutical kit according to any of the the preceding claims wherein the midodrine and/or desglymidodrine in fast onset formulation is present in an amount of from 0.2 mg to 10 mg, preferreably from 0.5 mg to 7.5 mg such as in an amount of 0.75 mg, 1 mg, 1.25 mg, 1.5 mg, 2. mg, 2.5 mg, 3 mg, 4 mg, or 5 mg.

61. A method for treating a patient suffering from orthostatic hypotension and/or urinary incontinence such as urinary stress incontinence, the method comprising administering once or twice daily an effective amount of midodrine and/or desglymidodrine in the form of a controlled release composition according to the pharmaceutical kit of any of claims 1-59 to a patient; and
further administering one or more fast onset formulations according to the pharmaceutical kit of any of claims 1-60 to a patient in need thereof

62. A method according to claim 61, wherein the administration of the controlled release composition takes place at wake-up time.

63. A method according to claim 61, wherein the administration of the controlled release composition takes place in the morning.

64. A method according to any of claims 61-63 wherein the fast onset formulation is administered upon observations of symptoms and/or when symptoms are expected.

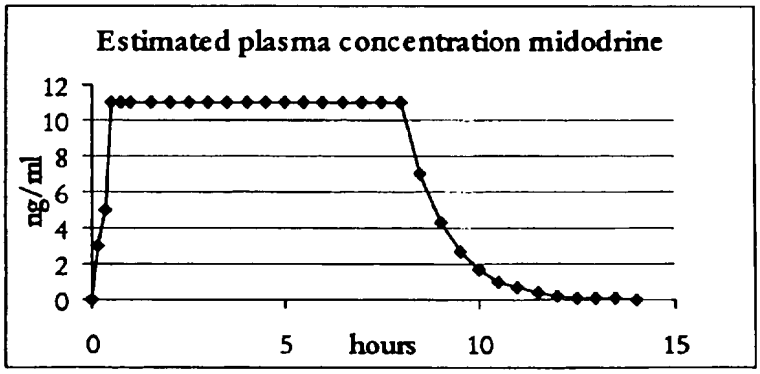



Fig. 1

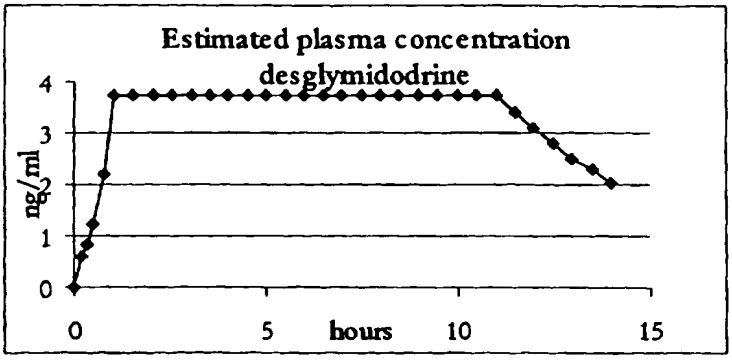



Fig. 2

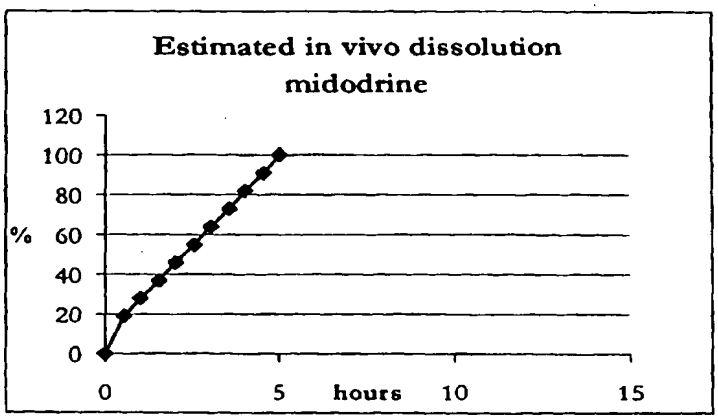



Fig. 3

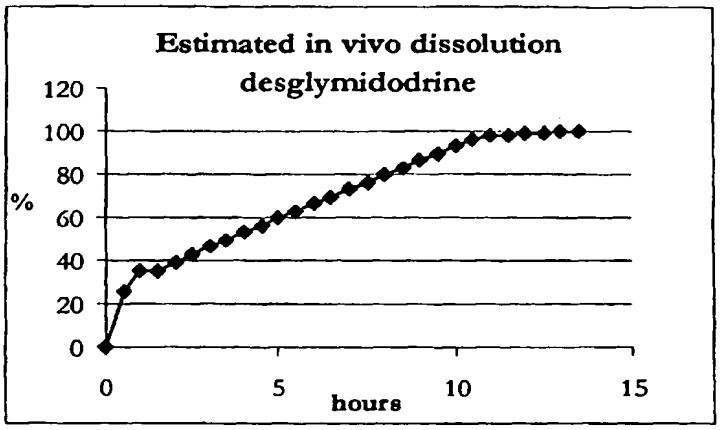



Fig. 4

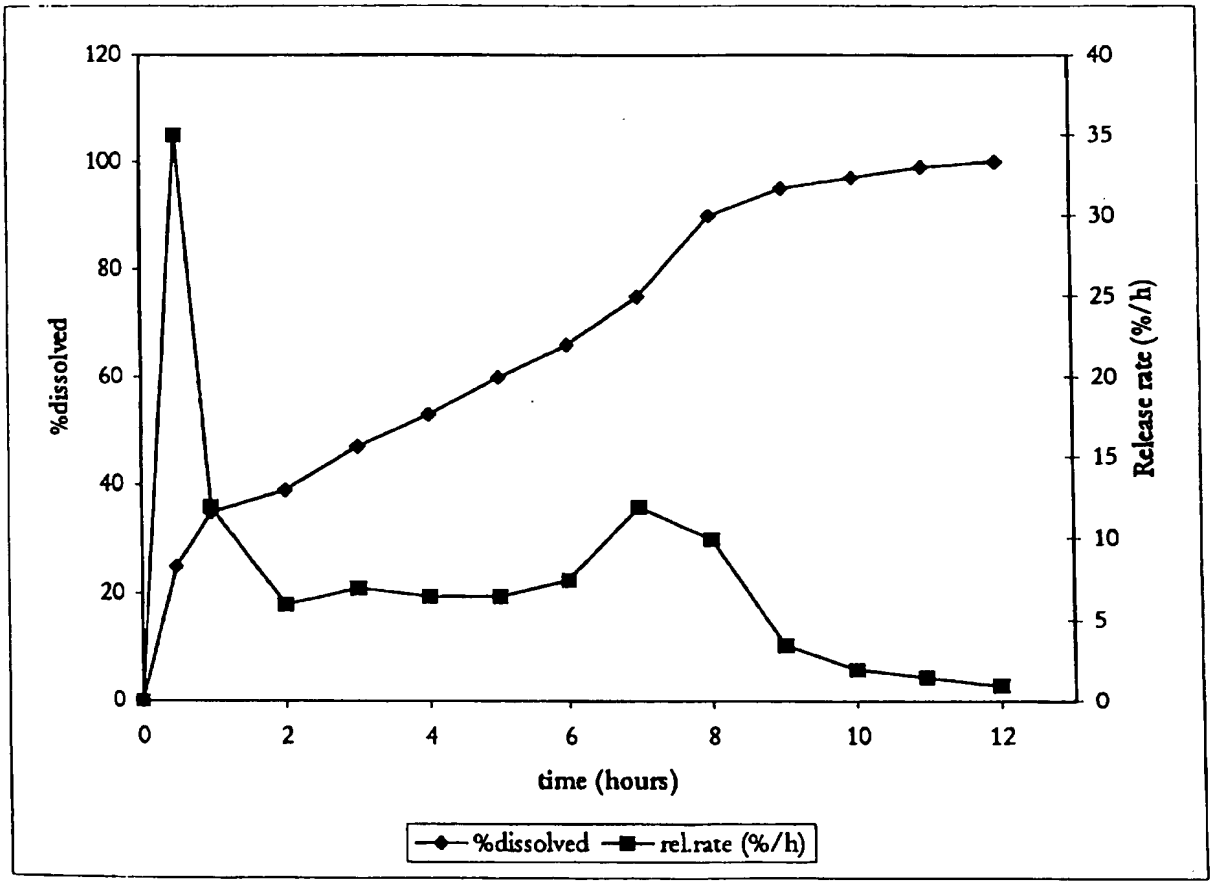
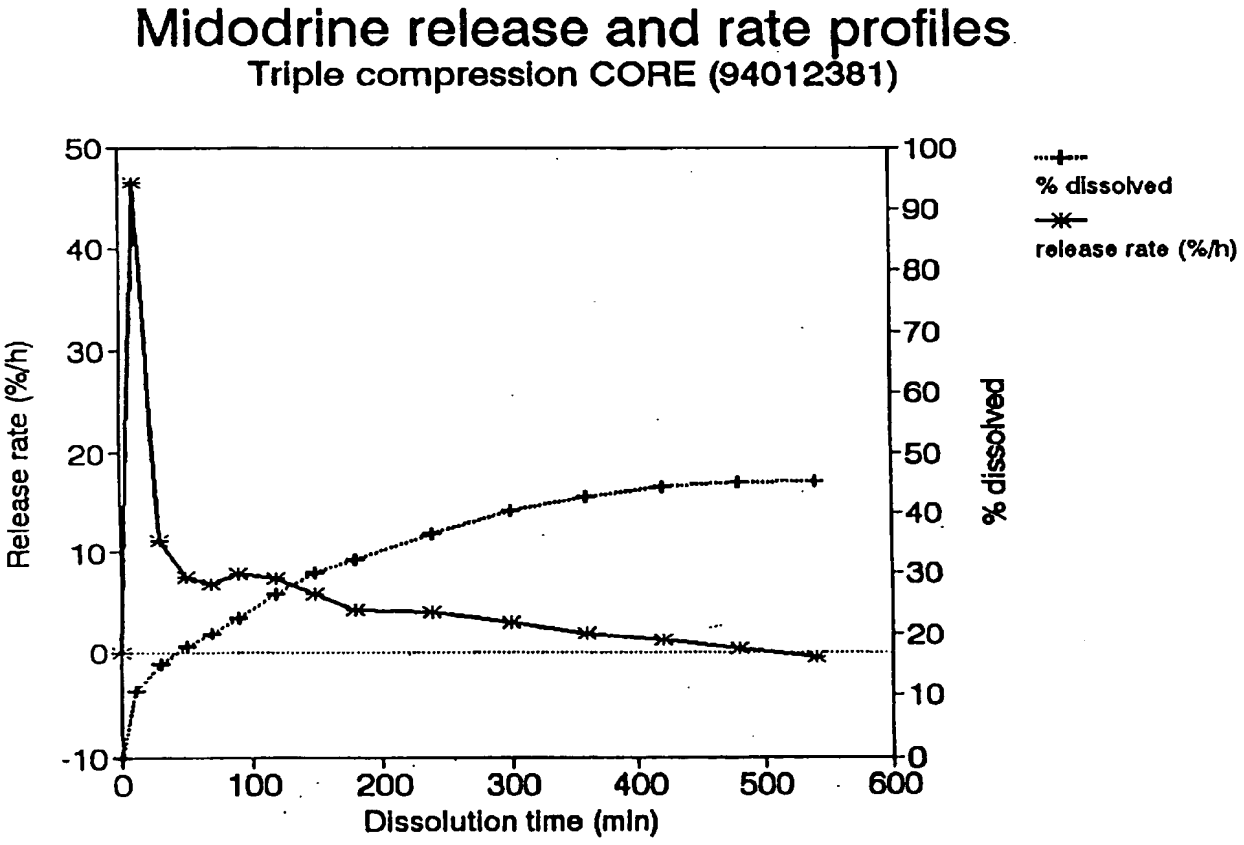
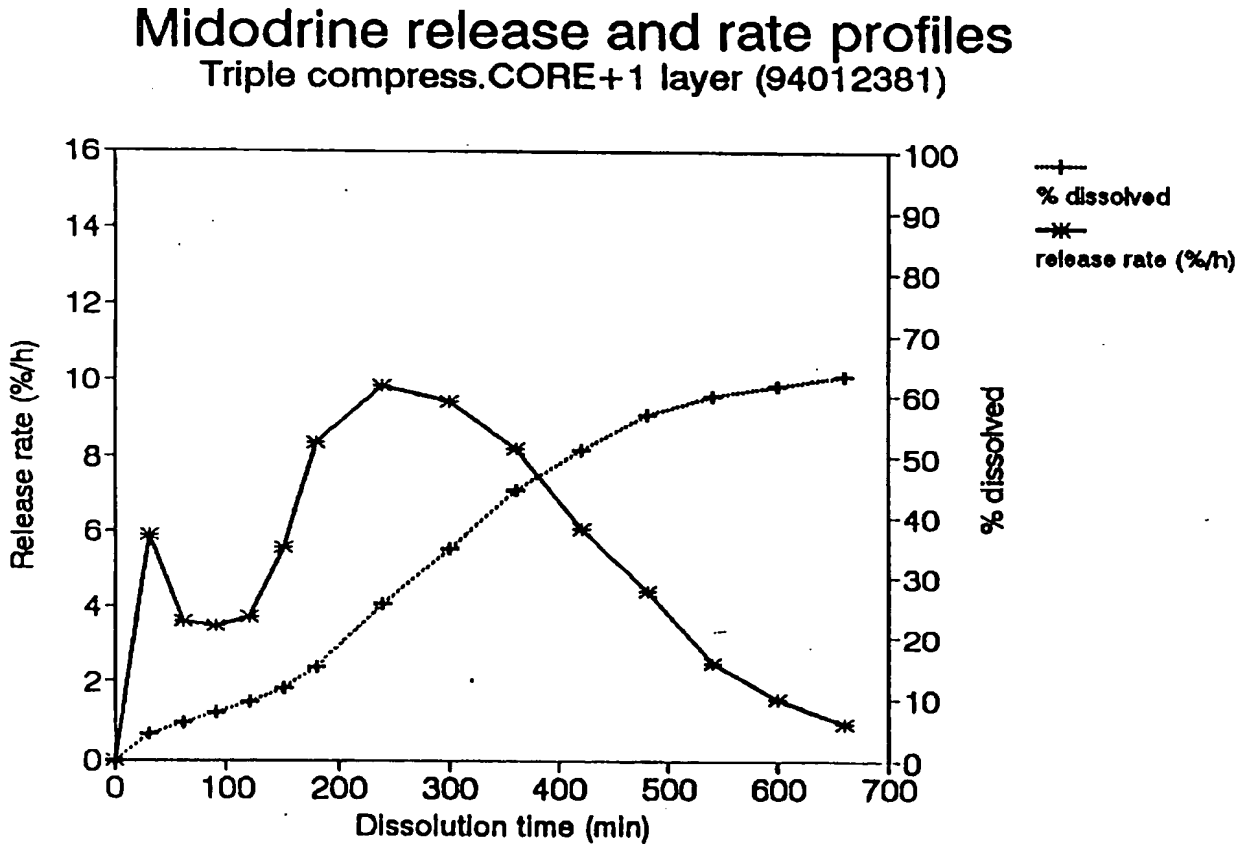



Fig. 5



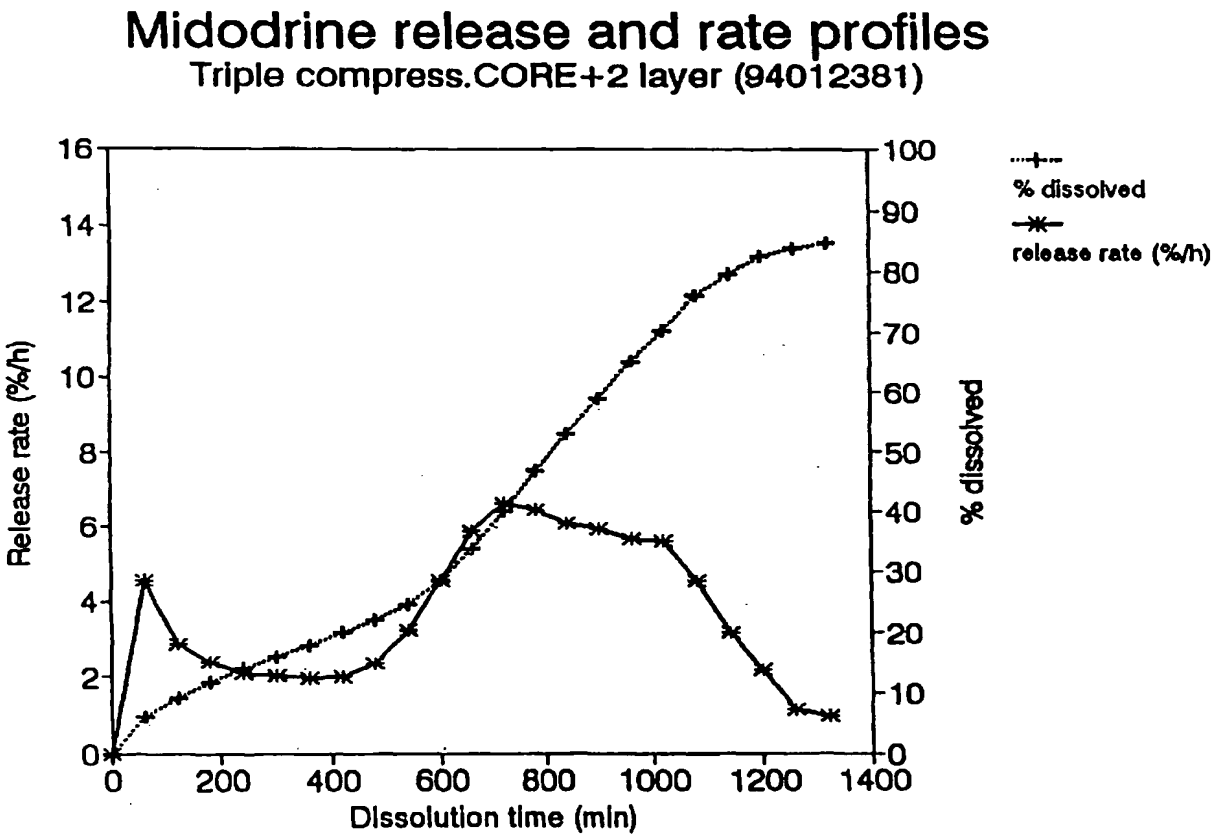

PLEASE NOTE: nominal amount sat at 10 mg

Fig. 6




PLEASE NOTE: nominal amount sat at 10 mg

Fig. 7




PLEASE NOTE: nominal amount sat at 10 mg

Fig. 8

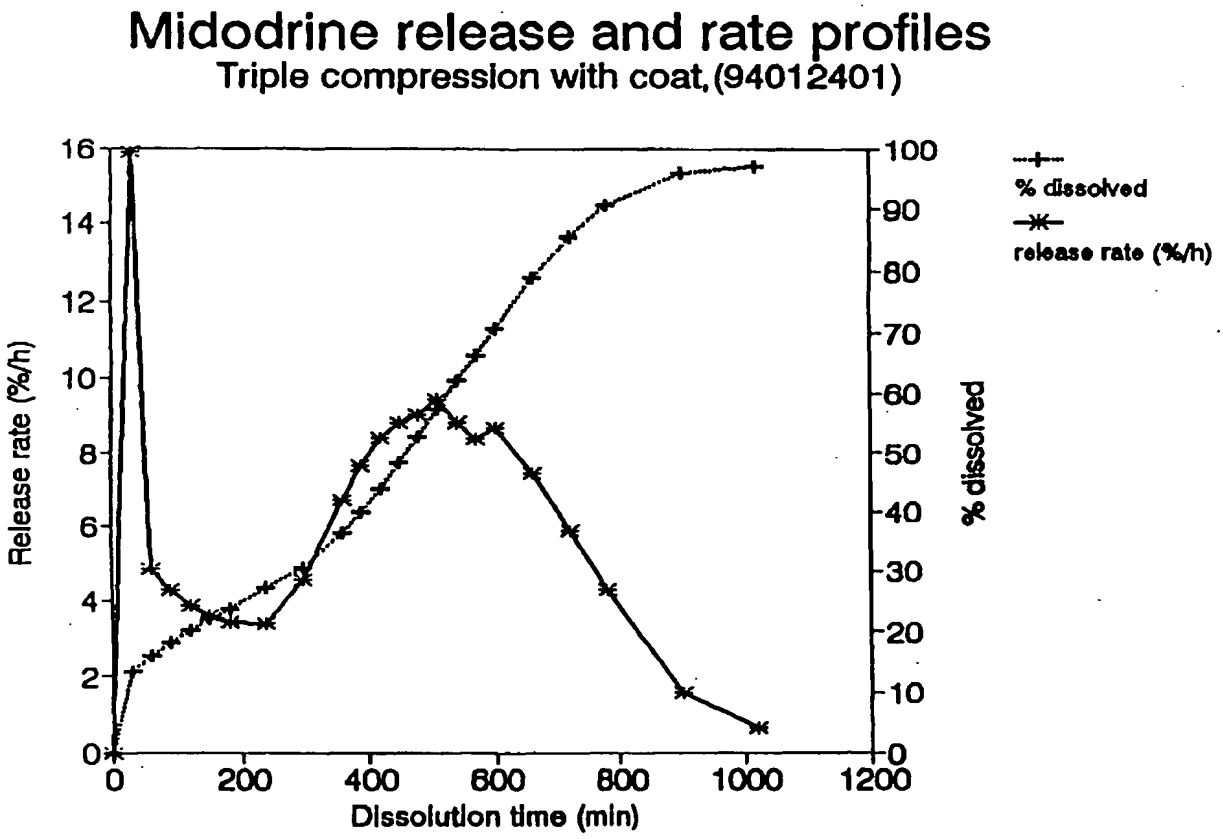
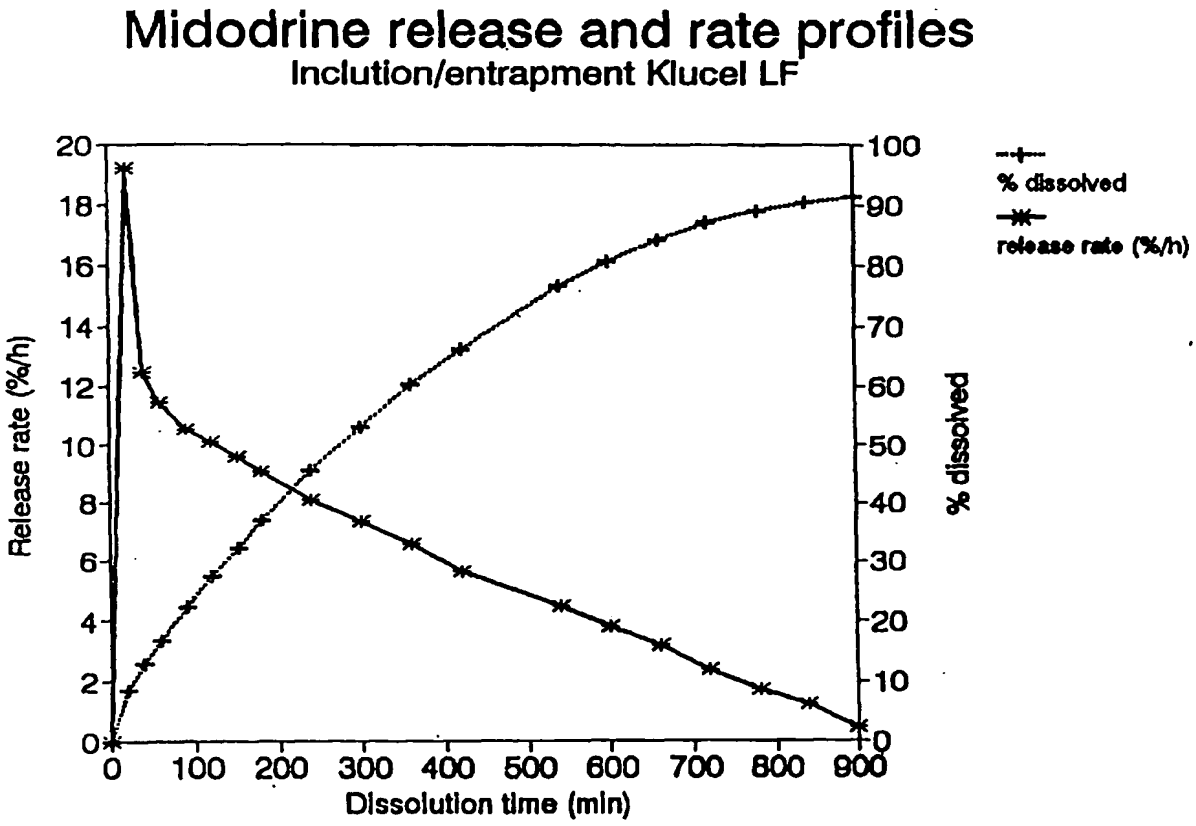
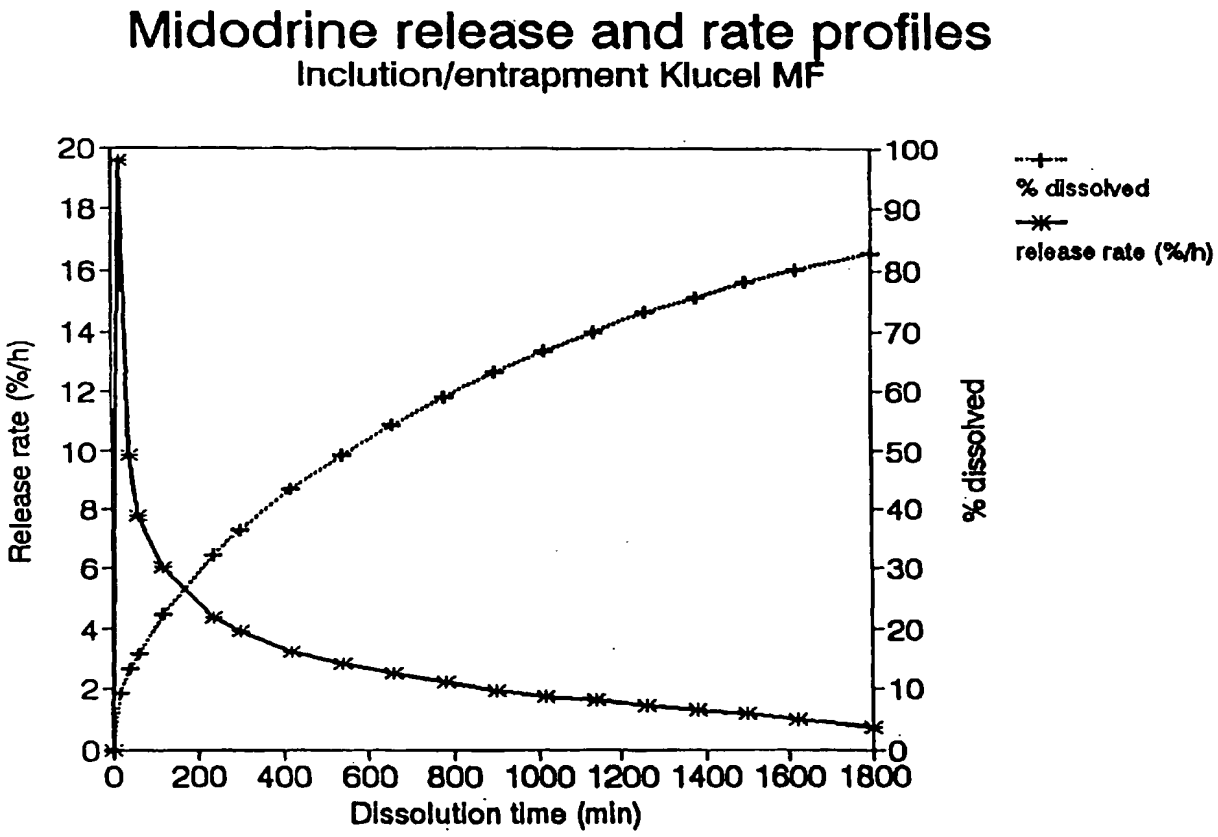



Fig. 9



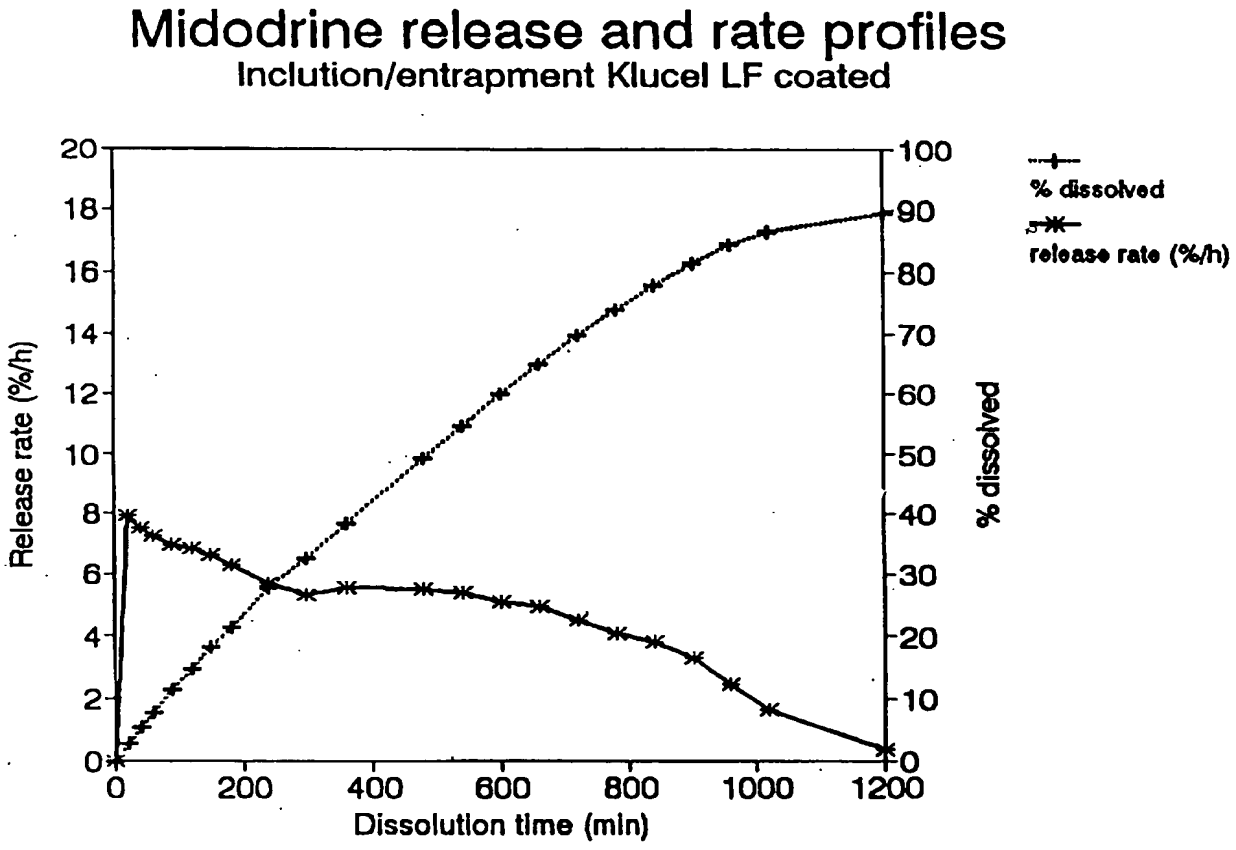

Please note: nominal amount 10 mg

Fig. 10



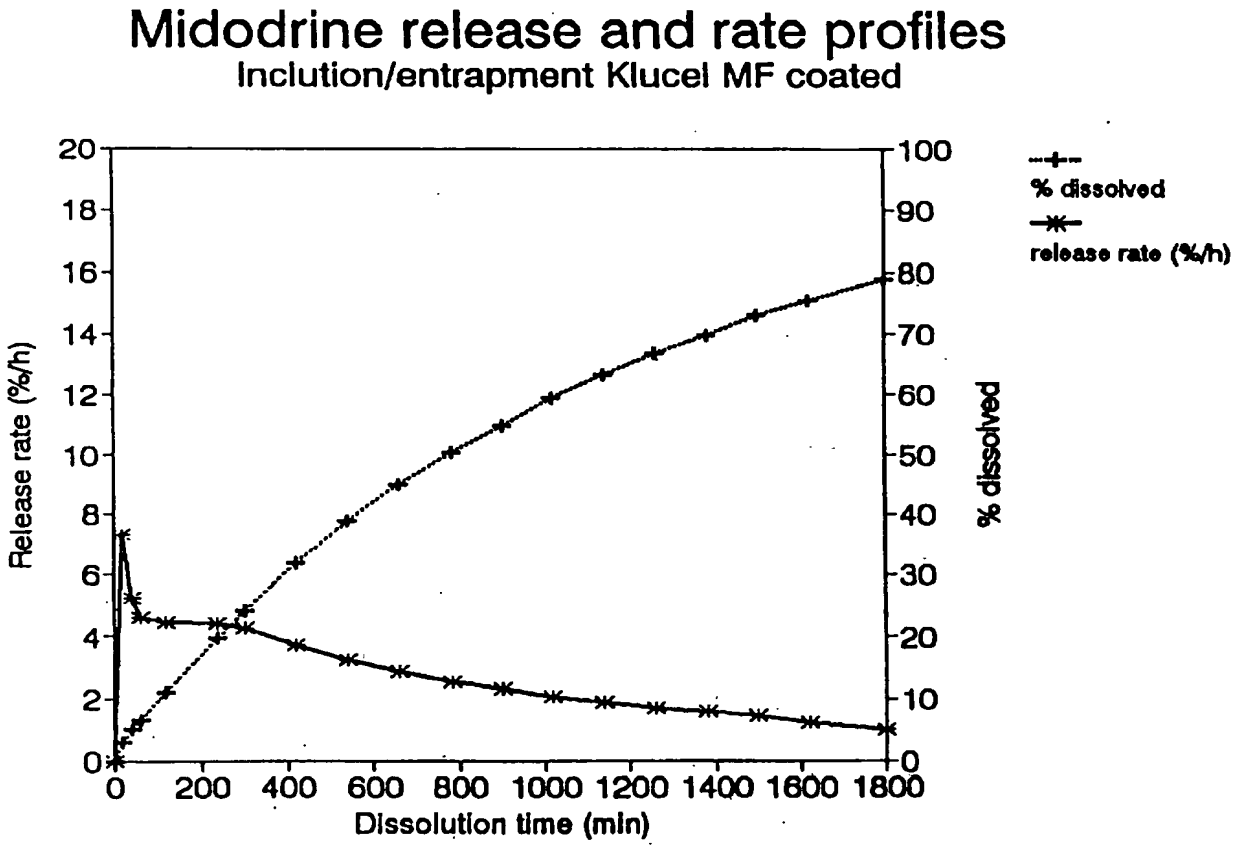

Please note: nominal amount 10 mg

Fig. 11



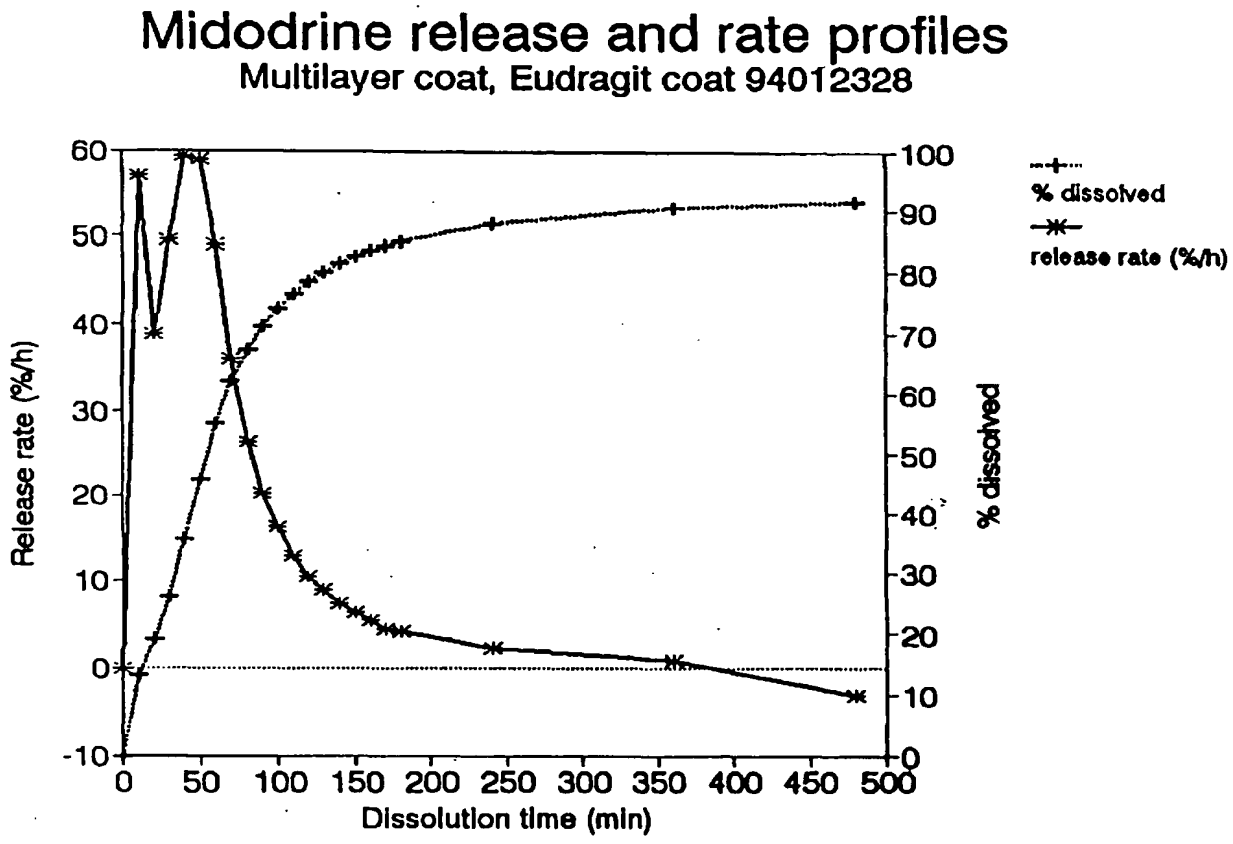

Please note: nominal amount 10 mg

Fig. 12



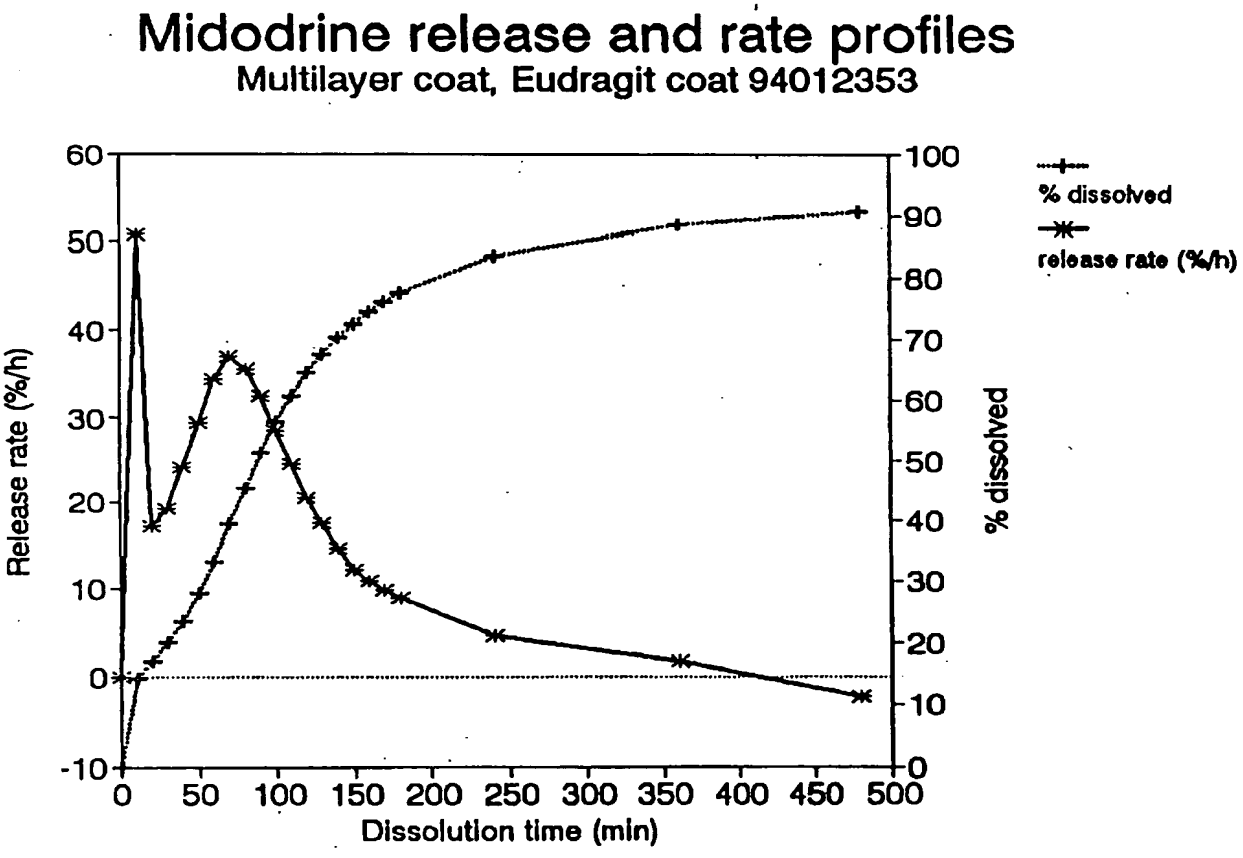

Please note: nominal amount 10 mg

Fig. 13



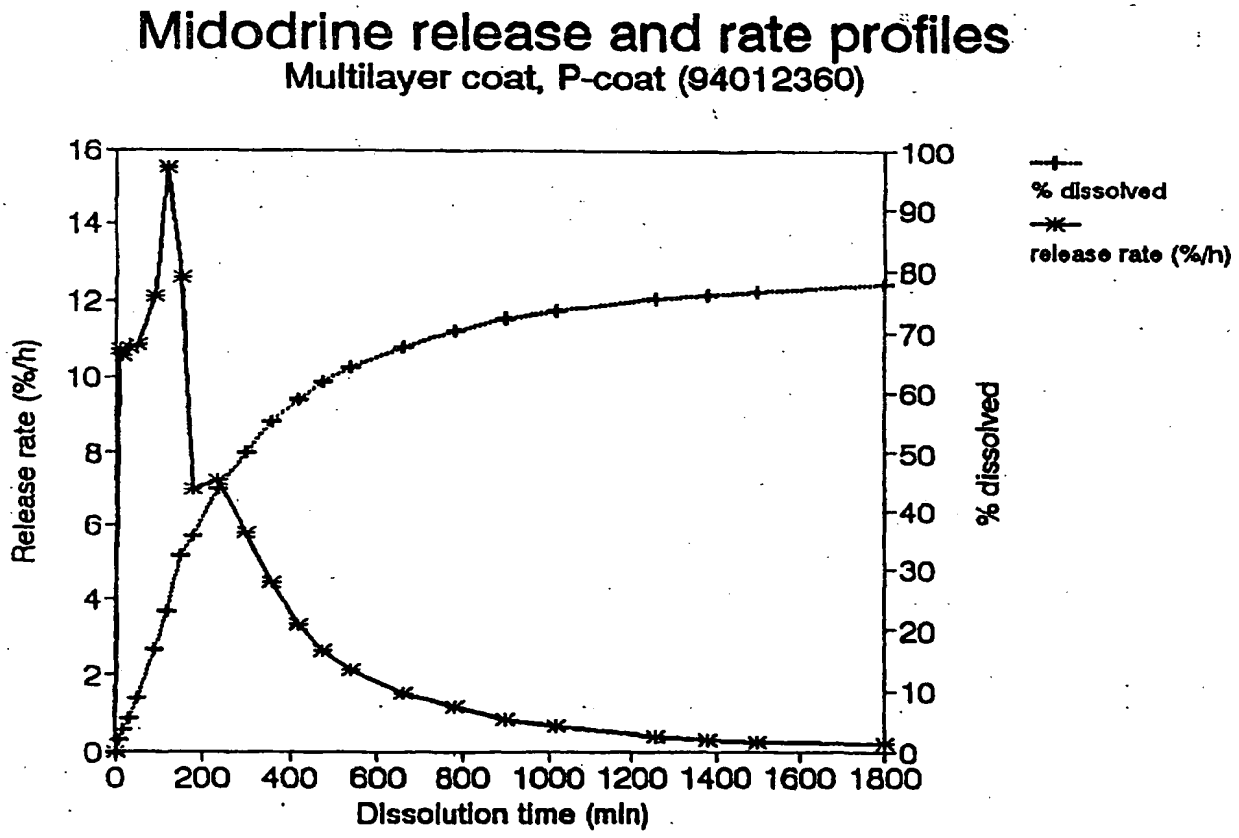

Please note: nominal amount 10 mg

Fig. 14




Please note: nominal amount 10 mg

Fig. 15




Please note: nominal amount 10 mg

Fig. 16